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Anesthesia and Analgesia

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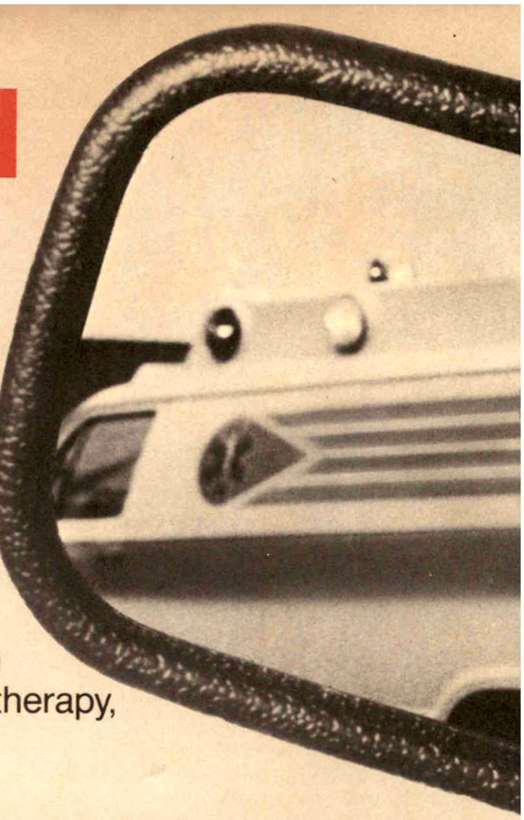
CORTICOID THERAPY IN CRITICAL CARE



Pharmacologic doses of corticoids have been used in the treatment of shock unresponsive to conventional therapy, if adrenocortical insufficiency exists or is suspected.

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ACTIONS—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

CONTRAINDICATIONS—Systemic fungal infections—Hypersensitivity to any component.

WARNINGS—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage In Pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALL IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

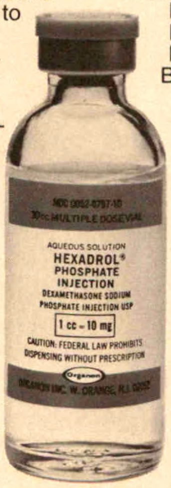
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

PRECAUTIONS—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid shou be administered concurrently.

There is an enhanced effect of corticosteroids in patients wit hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with oc lar herpes simplex for fear of corneal perforation.



100 mg

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, approrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

ADVERSE REACTIONS—

Fluid and electrolyte disturbances: Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

Musculoskeletal: Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

Dermatologic: Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

Neurological: Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

Endocrine: Menstrual irregularities; Development of Cushingoid state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; Increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Miscellaneous: Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

DOSAGE AND ADMINISTRATION—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.

CAUTION—Federal law prohibits dispensing without prescription.

HOW SUPPLIED—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25;
10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

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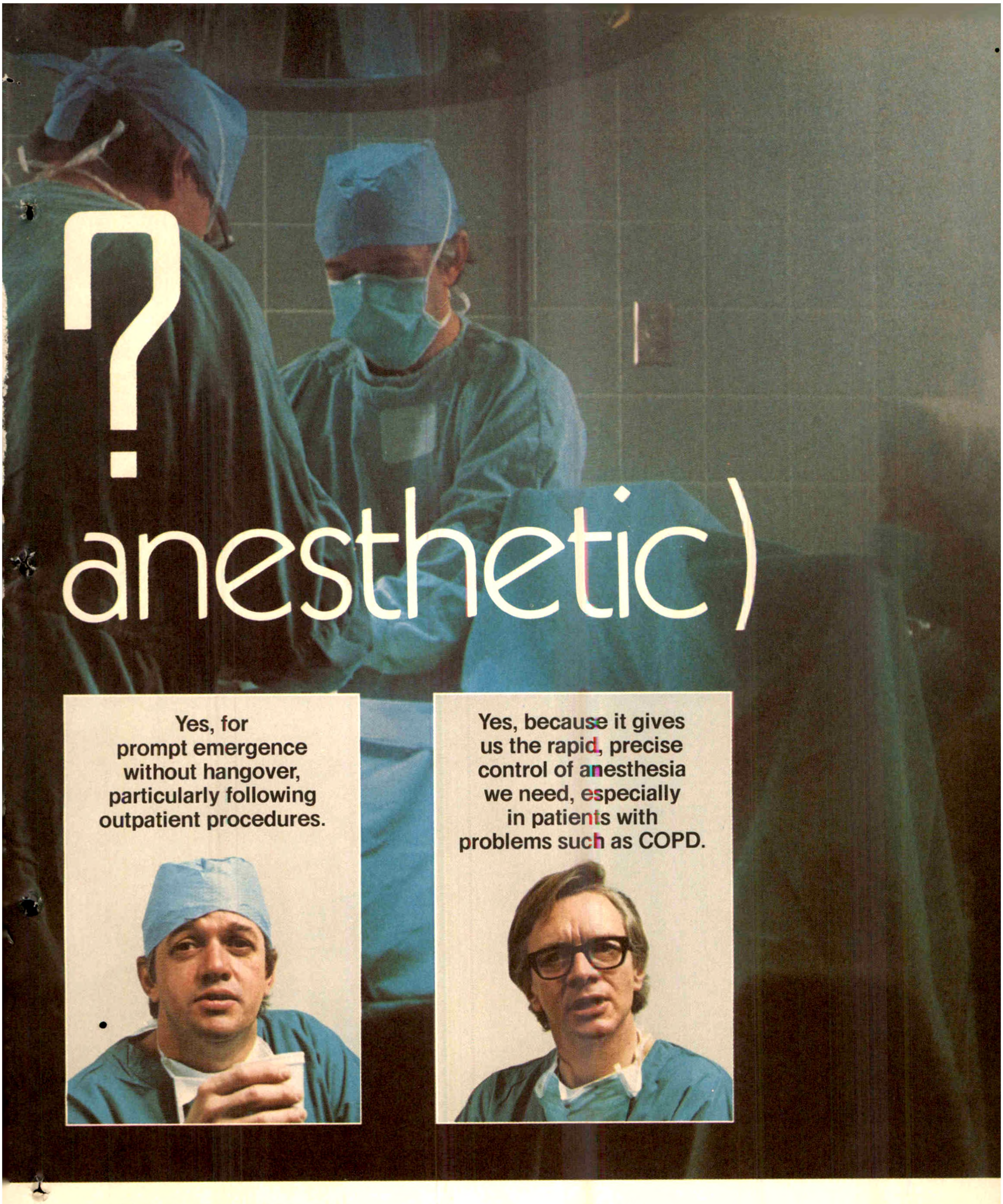
Ēthrane
(enflurane
Yes, for its inherent muscle-relaxant effect in cholecystectomies and other abdominal surgeries.
Yes, because it allows more latitude in our use of epinephrine for hemostasis, particularly in head and neck surgeries.

ĒTHRANE (enflurane)—with its low solubility in blood, inherent muscle-relaxant effect, and apparent lack of cardiac arrhythmic effect—offers you and your surgeons more control and more flexibility. And for patient comfort it provides smooth, rapid inductions, prompt emergence (with no need for narcotic reversal agents), and an early sense of alertness and well-being.

Facts About ĒTHRANE (enflurane)

- Blood-gas partition coefficient—1.9 @ 37°C.
- Compatibility with epinephrine—up to three 10 ml. injections of epinephrine solution (1:100,000 or 1:200,000) may be given within an hour.
- Concomitant muscle-relaxant dosage—(if needed) only ½ to ⅓ the usual requirements of nondepolarizing agents



Yes, for prompt emergence without hangover, particularly following outpatient procedures.

Yes, because it gives us the rapid, precise control of anesthesia we need, especially in patients with problems such as COPD.

New ĒTHRANE (enflurane) Compendium and Reference

Virtually all of the known facts about this remarkably versatile anesthetic—along with succinctly phrased, informative clinical data—are now available to you and your staff in the new, updated *ĒTHRANE (enflurane) Compendium and Reference*. Ask your OHIO Anesthetic Agents Representative for your copy or write to us in Madison. For a summary of complete usage information,

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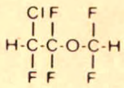
DESCRIPTION

ĒTHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$\mathrm{H{-}C(Cl)(F){-}C(F)(F){-}O{-}C(F)(F){-}H}$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \quad A = 7.967$$
$$B = -1678.4$$
$$T = {}^{\circ}C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ĒTHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ĒTHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ĒTHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

ACTIONS

ĒTHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ĒTHRANE are rapid. ĒTHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ĒTHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ĒTHRANE. ĒTHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ĒTHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ĒTHRANE anesthesia. ĒTHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ĒTHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ĒTHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ĒTHRANE.

Biotransformation of ĒTHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ĒTHRANE anesthesia in man in the absence of surgery. Thus ĒTHRANE does not depress this aspect of the immune response.

INDICATIONS

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ĒTHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ĒTHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ĒTHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ĒTHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ĒTHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ĒTHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ĒTHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ĒTHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ĒTHRANE mixture. In general, inspired concentrations of 3.5-4.5% ĒTHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ĒTHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ĒTHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

PACKAGING

ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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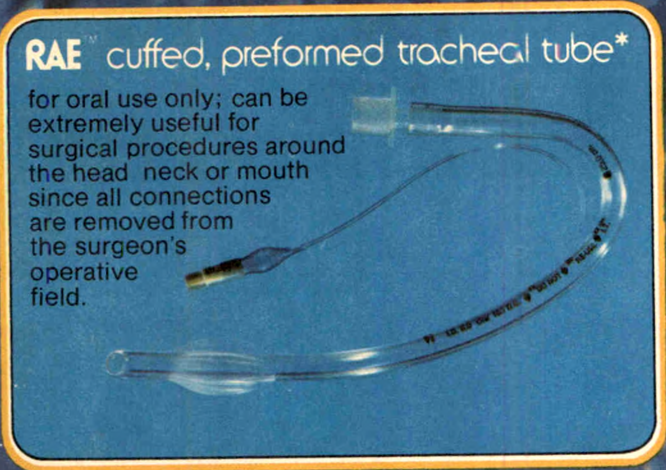
from National Catheter



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for oral use only; can be extremely useful for surgical procedures around the head neck or mouth since all connections are removed from the surgeon's operative field.

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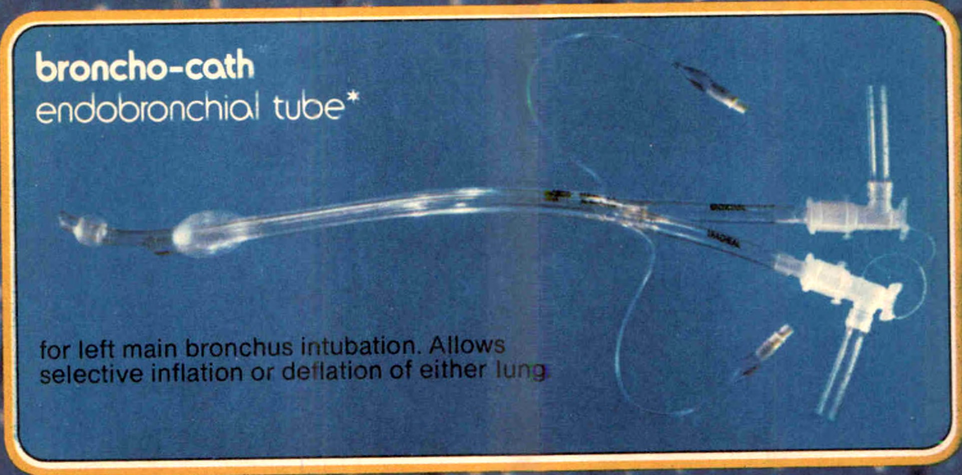

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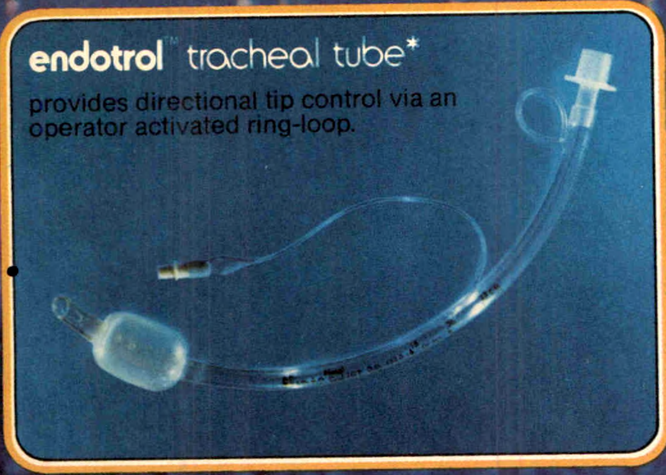
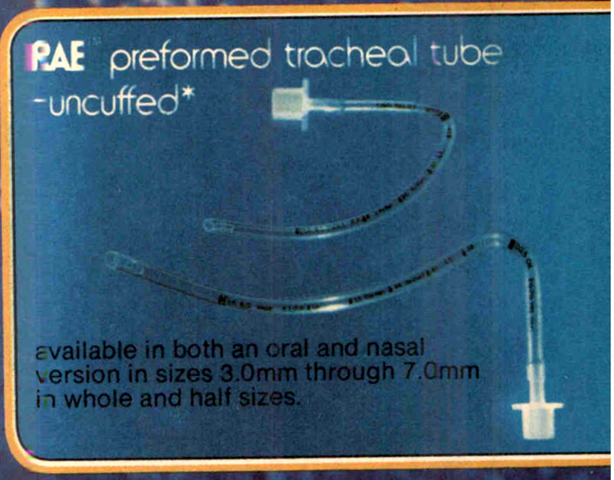
for left main bronchus intubation. Allows selective inflation or deflation of either lung



endotrol™ tracheal tube*

provides directional tip control via an operator activated ring-loop.



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available in both an oral and nasal version in sizes 3.0mm through 7.0mm in whole and half sizes.

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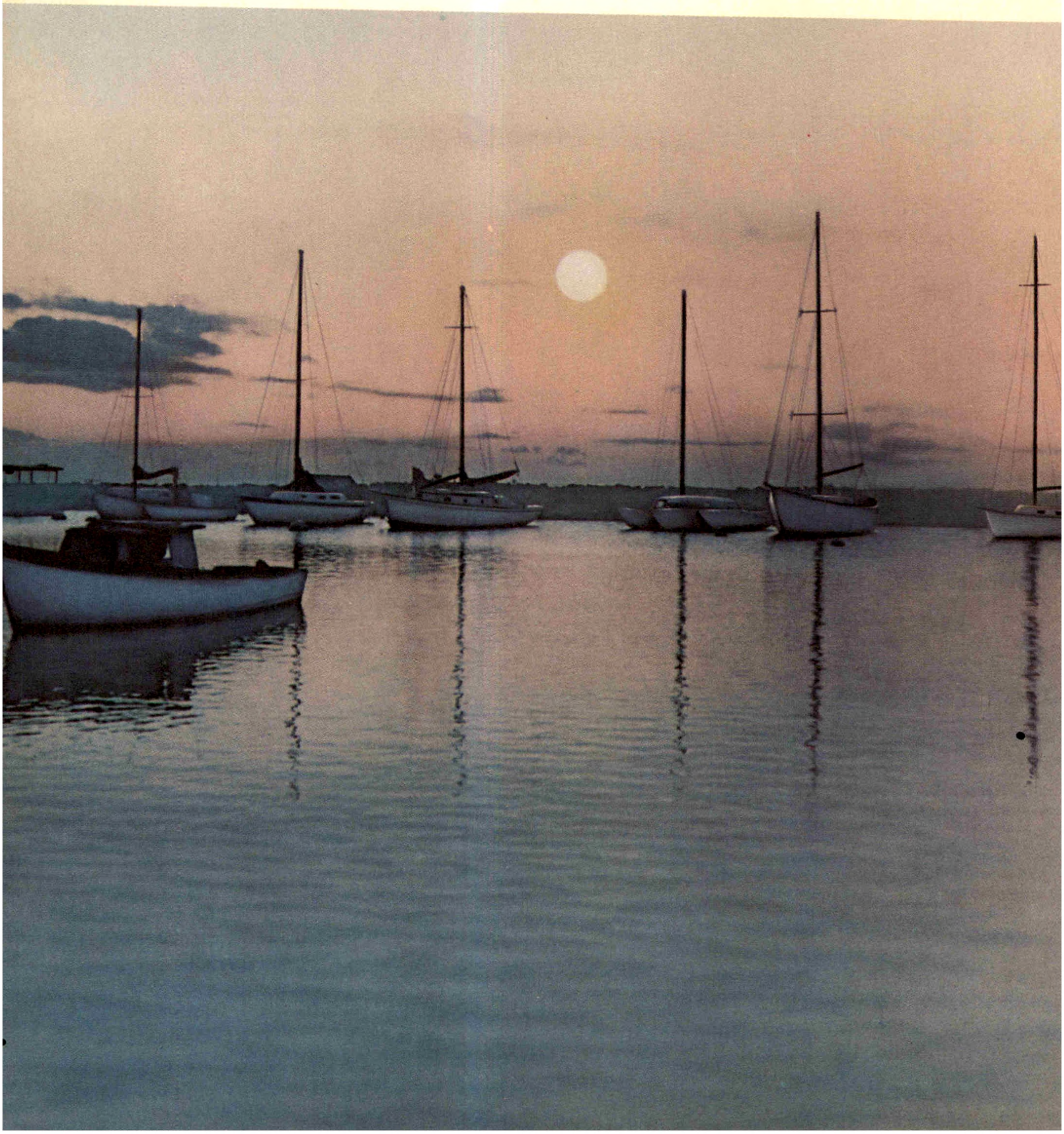
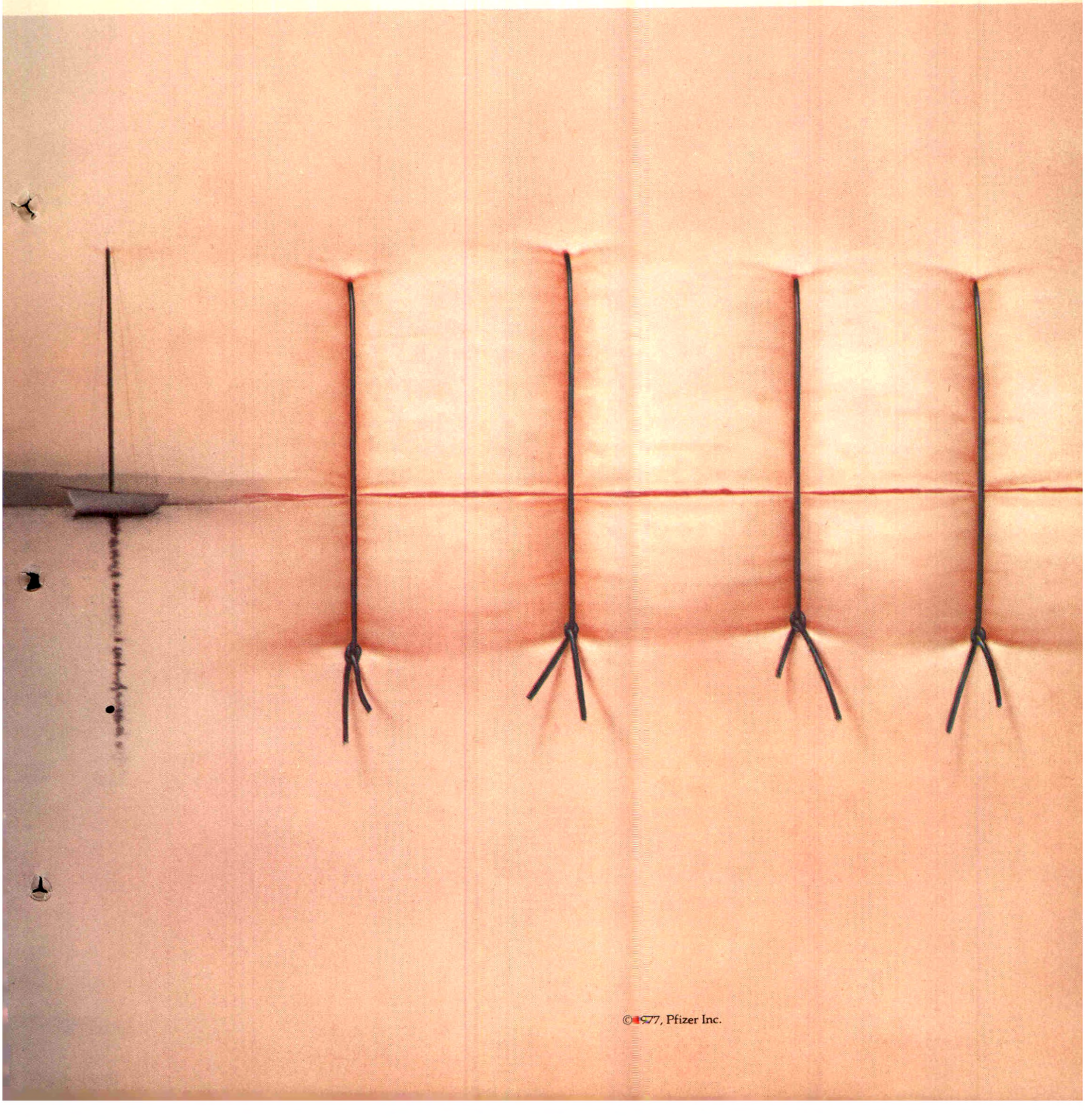


to surgery

Vistaril® I.M.
(hydroxyzine HCl)
—allays anxiety
—reduces narcotic requirements
—and controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions



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Vistaril® I.M.
(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

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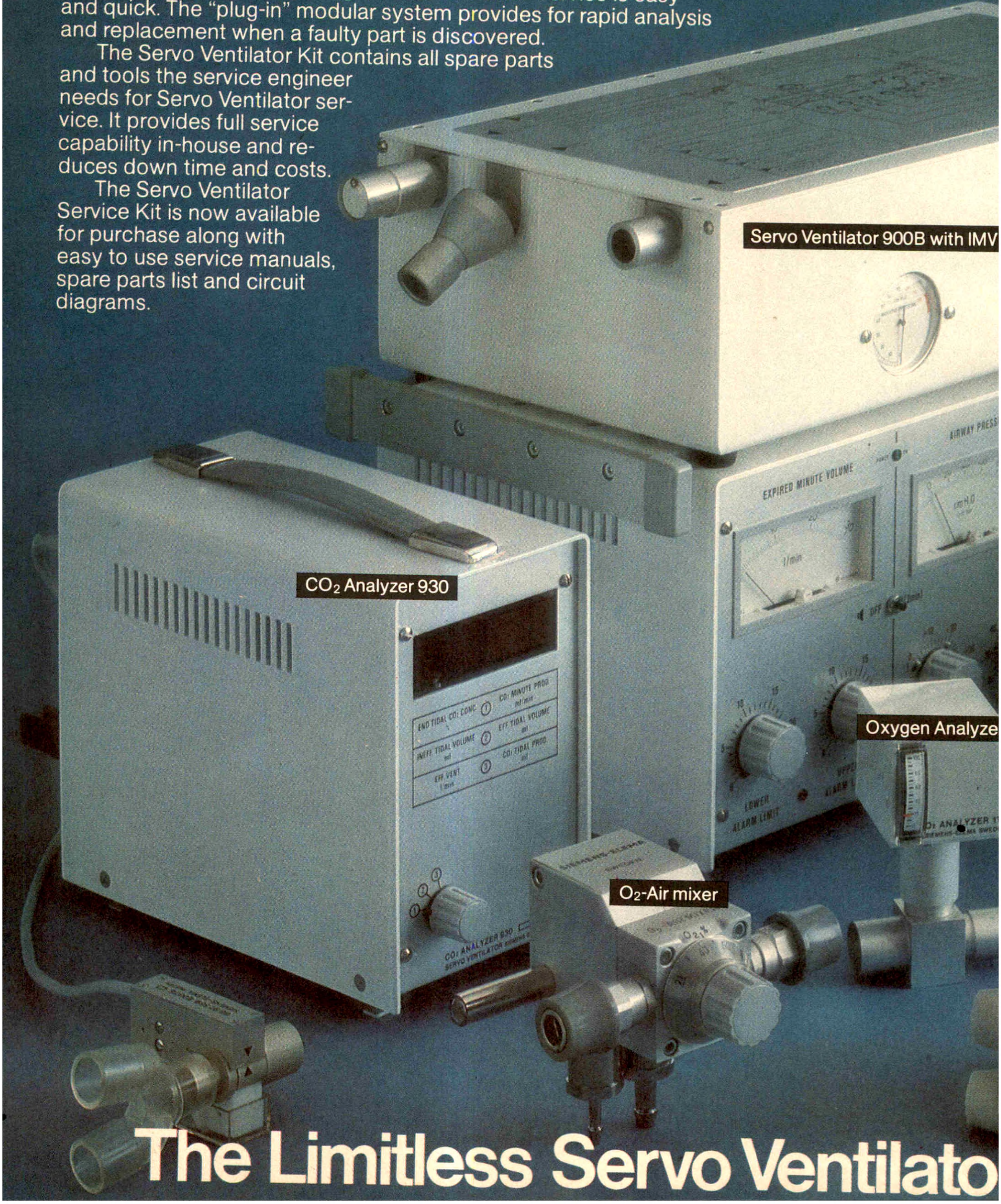

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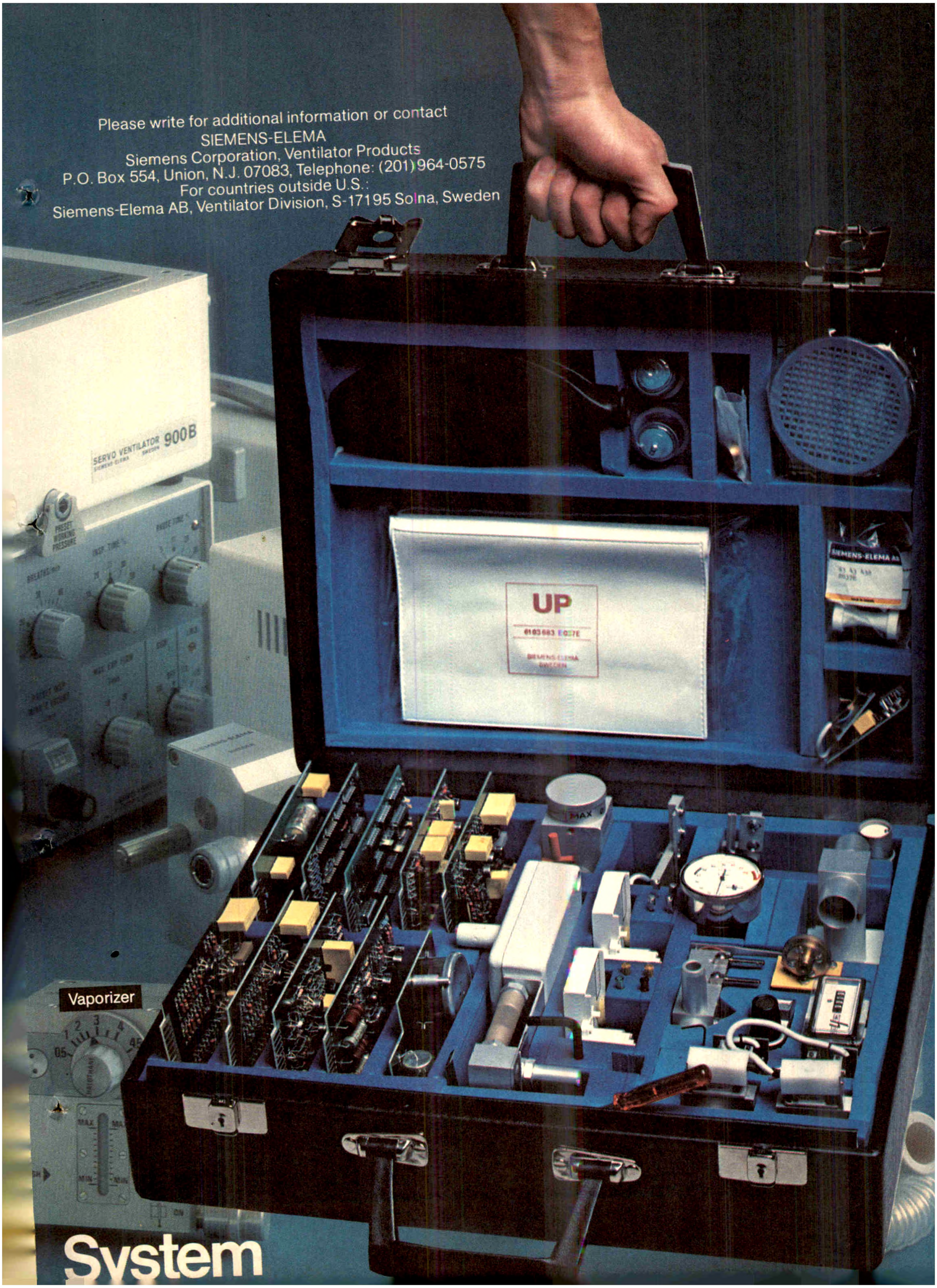
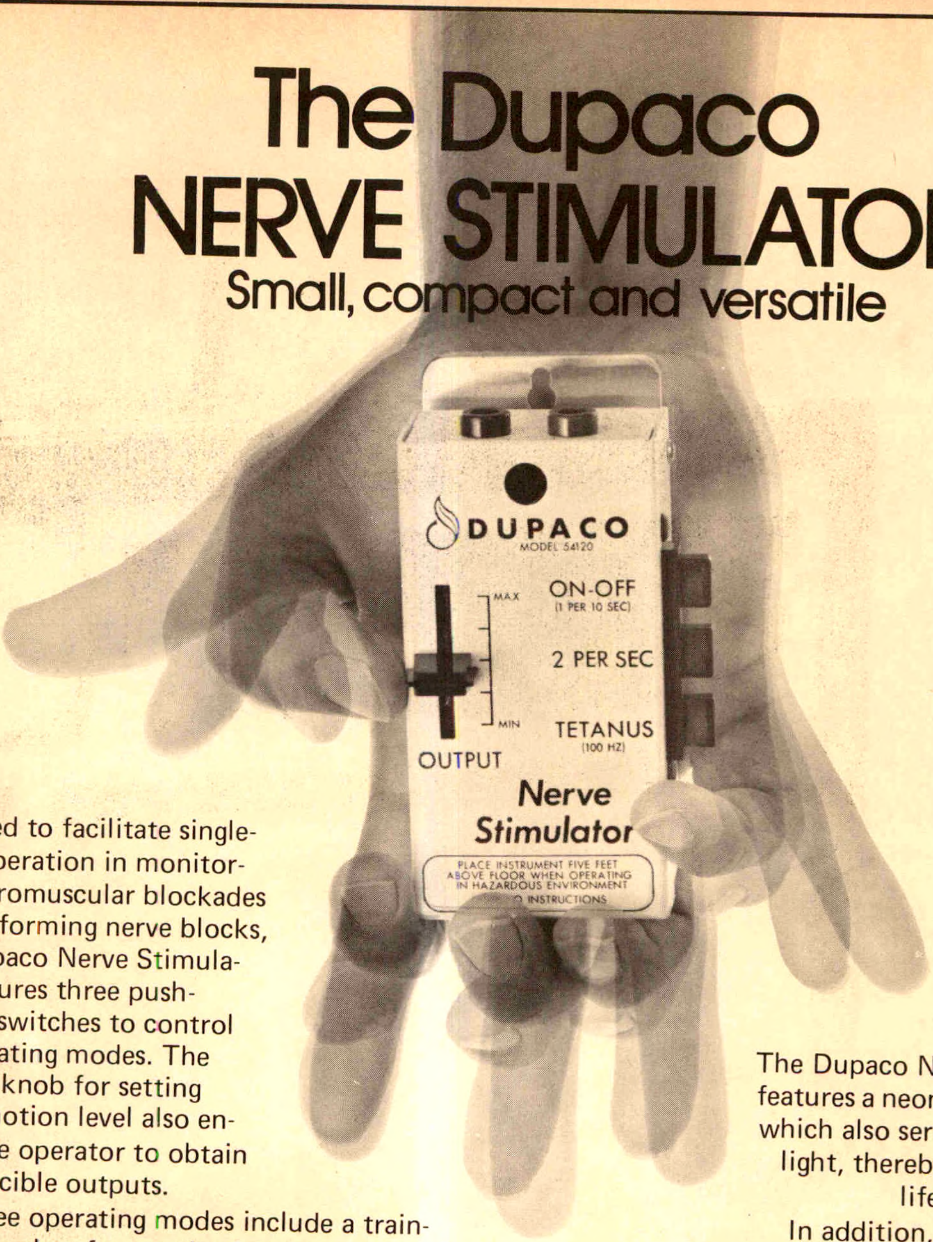


The Dupaco NERVE STIMULATOR

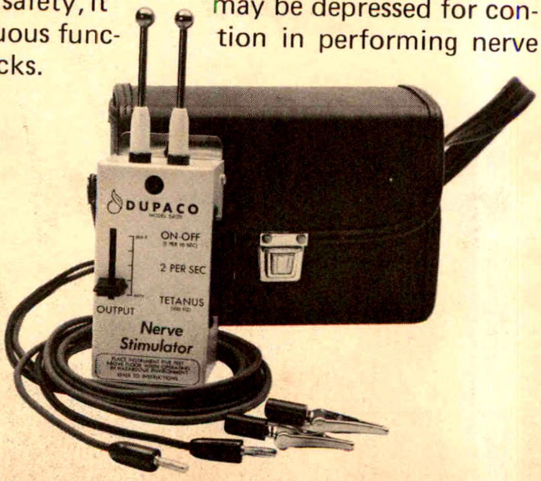
Small, compact and versatile



Designed to facilitate single-hand operation in monitoring neuromuscular blockades and performing nerve blocks, the Dupaco Nerve Stimulator features three push-button switches to control all operating modes. The control knob for setting linear motion level also enables the operator to obtain reproducible outputs.

The three operating modes include a train-of-four pulses for monitoring neuromuscular blockade, a tetanus frequency of 100 Hz for a larger margin of safety in ensuring adequate reversal of neuromuscular blockade, and a stand-by frequency of 0.1 Hz.

Although the train-of-four mode is momentary for safety, it may be depressed for continuous function in performing nerve blocks.



The Dupaco Nerve Stimulator features a neon pulse indicator which also serves as an on/off light, thereby extending the life of the battery.

In addition, a stainless steel clip doubles as battery compartment cover and a belt, linen or hook hanger.

The Dupaco Nerve Stimulator- small, compact and versatile because it has to be.

DUPACO

Post Office Box 98, San Marcos, Calif. 92069

In search of the ideal analgesic

1530
Opium comes into wide use

1803
Morphine isolated from opium

1945
Semisynthetics and synthetics gain acceptance

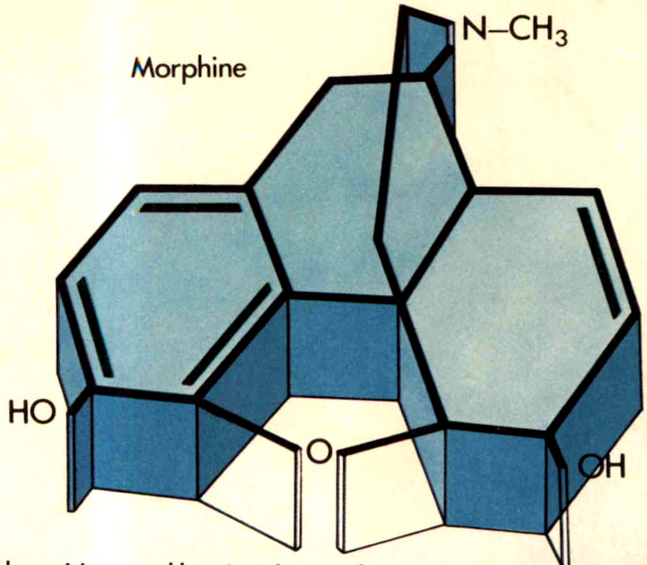
1967
The age of nonnarcotic analgesics dawns

and new in...

1978

Now... in moderate to severe pain Stadol® IM IV (butorphanol tartrate)

Bristol Laboratories is pleased to announce a new, extensively studied,[1-39] nonnarcotic, parenteral agent that comes closer to the ideal analgesic—combining a high degree of potency in the relief of moderate to severe pain, with a low potential for undesirable side effects.

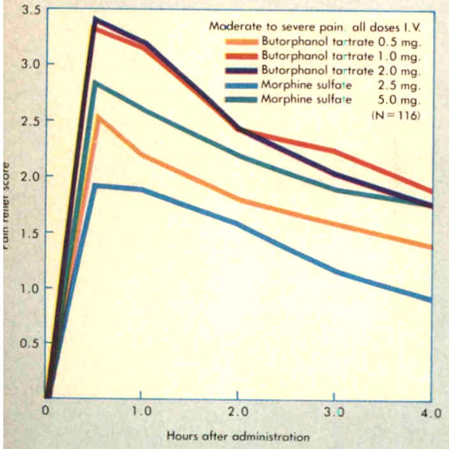


Important new option when potent parenteral analgesics are indicated

- Standard doses of Stadol are as effective in relieving pain as standard doses of both morphine[1-4] and meperidine.[5-7, 37]
- By either I.M. or I.V. route—provides prompt onset of analgesia, achieves peak activity rapidly, maintains effects for 3–4 hours.
- Distinguished by its favorable side effects profile,[1-16, 31-33, 36, 37]—low physical-dependence liability, limited respiratory depressant effect, little nausea and vomiting, and low incidence of CNS effects other than sedation.
- 2 mg. of Stadol produces an order of respiratory depression similar to that caused by 10 mg. of morphine. In contrast to morphine, increasing Stadol doses yield greater analgesic effect,[9] without appreciably increasing liability for respiratory depression.[16]
- The low addictive potential of Stadol[24] is underscored by its narcotic antagonist properties.

Stadol is not recommended for patients physically dependent on narcotics or with significant previous narcotic experience. Its use in such patients, without prior detoxification, will result in induction of withdrawal reactions.

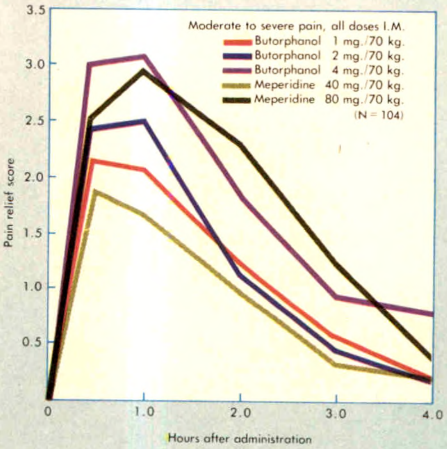
Unsurpassed pain relief



Average mean pain relief scores
n response to butorphanol tartrate
nd morphine sulfate

n this study "... butorphanol tartrate .5 mg produced greater relief than norphine sulfate 2.5 mg and butorhanol tartrate 1.0 and 2.0 mg produced greater relief than morphine sulfate .0 mg." (DelPizzo[1])

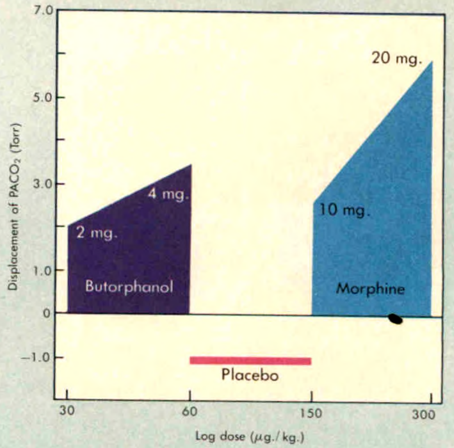
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate
and meperidine hydrochloride

In moderate to severe pain, butorphanol tartrate provided relief "... that was not statistically distinguishable from that achieved with 80 mg/70 kg meperidine." (Gilbert et al[5])

Limited respiratory depressant effect

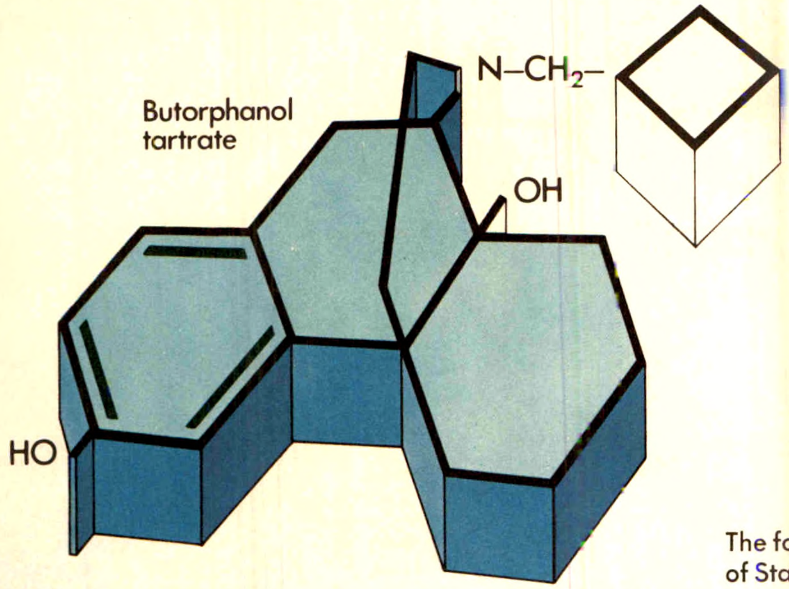


Log dose PACO2 displacement curves

In this graph based on alveolar carbon dioxide tension ($PACO_2$) measurements, the flatter the curve, the less respiratory depression. "The flat dose-response curve ... of butorphanol may indicate that, because of its antagonistic properties, there is a limit to its respiratory depressant effects. (Adapted from Nagashima et al[16]) **Unlike morphine with its steep dose-response curve, the magnitude of respiratory depression does not increase in a dose-related manner with Stadol, within the range of recommended doses.**

Please see last page for a brief summary of prescribing information.

closer to the ideal parenteral analgesic



new Stadol® IM IV

(butorphanol tartrate)

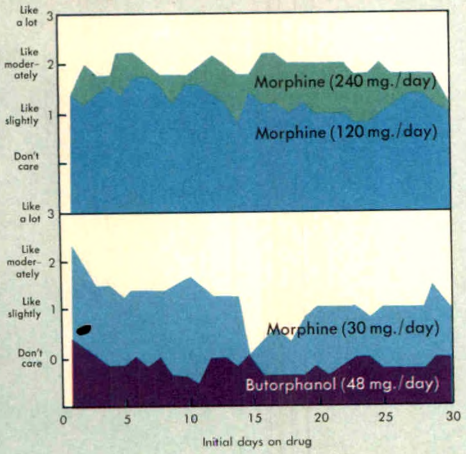
another step closer to the ideal

The following table shows a side-by-side clinical comparison of Stadol with both morphine and meperidine.

Clinical parameters	Meperidine	Morphine	Stadol
Classification	narcotic	narcotic	**nonnarcotic**
Indication	moderate to severe pain	moderate to severe pain	**moderate to severe pain**
Standard I.M. dose	75–100 mg.	8–10 mg.	**2 mg. (1 to 4 mg.)**
Standard I.V. dose	50–100 mg.	4–10 mg.	**1 mg. (0.5 to 2 mg.)**
Usual route of administration	I.M./I.V.	I.M./I.V.	**I.M./I.V.**
Onset of pain relief	30 minutes I.M., very rapidly I.V.	30 minutes I.M., very rapidly I.V.	**less than 30 minutes I.M., very rapidly I.V.**
Peak analgesic activity	within 1 hour I.M., within 30 minutes I.V.	within 1 hour I.M., within 20 minutes I.V.	**within 1 hour I.M., within 30 minutes I.V.**
Duration of pain relief I.M./I.V.	slightly less than morphine	about 4 hours	**3–4 hours**
Addicting potential	high	high	**low**
Respiratory effects	dose-related depression	dose-related depression	**limited depression—no appreciable dose-related increase within the range of recommended doses.**

Data for this table were obtained from: Jaffe, J. H. and Martin, W. R.: Narcotic analgesics and antagonists, in The Pharmacological Basis of Therapeutics (Goodman, L. S. and Gilman, A., eds.), ed. 5, New York, Macmillan, 1975, pp. 245–283; AMA Drug Evaluations, ed. 3, Chicago, 1977, pp. 325–339; and from manufacturer recommendations.

Low physical-dependence liability



Preference scores completed by subjects during chronic butorphanol tartrate administration compared with scores from three other groups of subjects receiving 30, 120 and 240 mg. of morphine daily. (Adapted from Jasinski et al[24])

BRISTOL™ BRISTOL LABORATORIES
Div. of Bristol-Myers Company
Syracuse, New York 13201

In moderate to severe pain...
New, parenteral

new Stadol® IM IV
(butorphanol tartrate)

INDICATIONS AND USAGE— (1) 8/18/78

Stadol is recommended for the relief of moderate to severe pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients physically dependent on narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical-dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head injury and increased intracranial pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular effects: Because Stadol increases the work of the heart, especially the pulmonary circuit (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain respiratory conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired renal or hepatic function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage in pregnancy: The safety of Stadol for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in labor and delivery: Safety to the mother and fetus following administration of Stadol during labor and delivery has not been established.

Usage in nursing mothers: The use of Stadol is not recommended in nursing mothers since it is not known whether this drug is excreted in human milk.

Pediatric use: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS effects: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic effects: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors, and assisted or controlled respiration.

DOSAGE AND ADMINISTRATION—*Adults:* Intramuscular—The usual recommended single dose is 2 mg. This may be repeated every three to four hours, as necessary. The effective dosage range, depending on the severity of pain, is 1 to 4 mg. repeated every three to four hours. At this time, there is insufficient clinical data to recommend single doses beyond 4 mg.

Intravenous—The usual recommended single dose for intravenous administration is 1 mg. repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg. repeated every three to four hours.

Children: Since there is no clinical experience in children under 18 years, Stadol is not recommended in this age group.

Storage conditions: When stored at room temperature, the stability of the solution in vials is 2 years.

SUPPLY—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, 2 mg. per ml., 2-ml. vial; 1 mg. per ml., 1-ml. vial; 2 mg. per ml., 1-ml. vial; 2 mg. per ml., 10-ml. multi-dose vial.

NDC 0015-5644–2 mg. per ml., 2-ml. vials
NDC 0015-5645–1 mg. per ml., 1-ml. vials
NDC 0015-5646–2 mg. per ml., 1-ml. vials
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For information on package sizes available, refer to the current price schedule.

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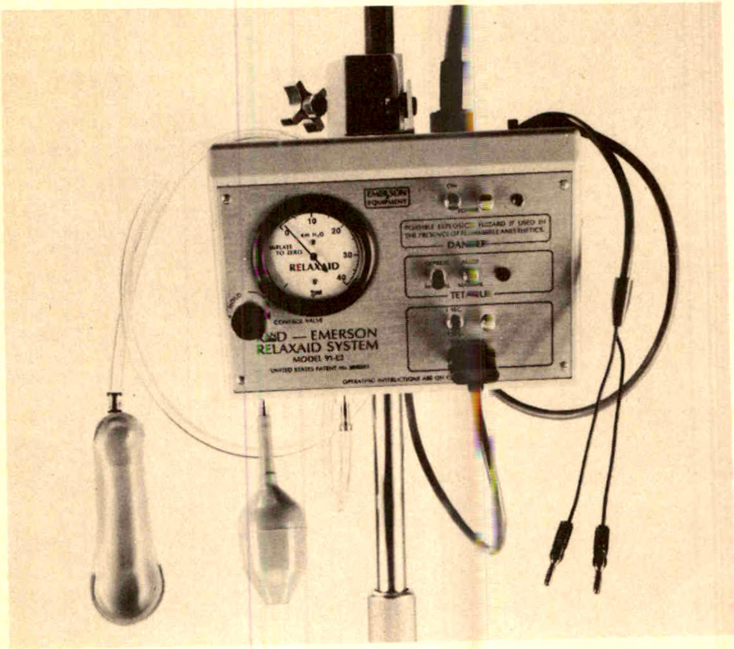
R^AN^D-EMERSON RELAXAID™



for CORRECT RELAXANT DOSAGE—
AVOIDANCE OF OVERDOSE—
PROMPT RECOVERY—

The stimulator is programed to deliver pulses, through electrodes, to the ulnar nerve. A flexible pneumatic bulb is placed in the patient's hand, with his fingers held against it by tape. The bulb is then air-filled to a pressure of 20 cm. H_2O. As the fingers flex, even slightly, compression of the bulb is registered on an aneroid gauge. The pattern of these responses keeps the anesthetist informed of the relaxant's effectiveness.

The more precise monitoring provided by the RELAXAID™ enables relaxant levels to be kept adequate but without overdose. During recovery the RELAXAID™ shows the return of strength to the patient's muscles.

Please request Form 91-E2

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YOU KNOW THE POSITIVE SIDE OF
NARCOTIC-SUPPLEMENTED ANESTHESIA..
TITRATES THE RESPIRATORY DEPRESSION OUT

NARCAN®

naloxone HCl

NEUTRALIZES THE NEGATIVE

NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

Useful when narcotic/N_2O anesthesia is employed

Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism

The duration of activity of some narcotics may exceed that of NARCAN® Observe the patient closely and give repeat doses of NARCAN® if needed.

Also available, NARCAN® NEONATAL naloxone HCl

Please see next page for complete prescribing information.

Endo Laboratories, Inc.
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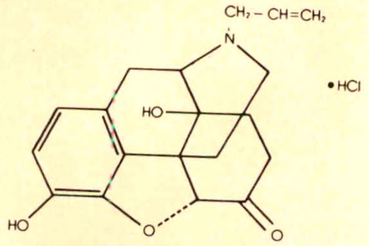
NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088.

OF NARCOTIC-SUPPLEMENTED ANESTHESIA

NARCAN®

naloxone HCl

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ±5 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

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EDO-050N

May, 1977

NEW

MEDA SONICS

MODEL P81 PROBE AND VERSATONE DOPPLER MODEL D8

Now dramatically reduces interference from electrocautery equipment.

The Model P81 probe is designed to detect venous air embolism during any surgical procedure in which this is a potential complication. This probe and the VERSATONE® Doppler are now manufactured using special shielding techniques to substantially reduce electrocautery interference. This permits the anesthesiologist to continue monitoring Doppler sounds of heart motion even while the electrocautery is being used.

The potential complication of venous air embolism has received considerable recognition in the literature. Michenfelder, et. al.(1), have recommended early diagnosis as the most effective means of preventing serious sequelae from air embolism during neurosurgical procedures performed in the upright position. The Model P81 probe provides a continuous Doppler signal which varies in audible pitch in response to heart and blood flow motion. Distinctive, abrupt changes from the normal sounds are caused by emboli. A tape cassette recording is available on request from MedSonics.

1. Michenfelder, J.D., et. al., "Evaluation of an Ultrasonic Device (Doppler) for the Diagnosis of Venous Air Embolism." Anesthesiology, 36, 2 (February 1972).

CAUTIONS AND CONSIDERATIONS – The ultrasound method of air embolism detection is subject to both false positive and false negative indications. It should not be the only step taken to diagnose venous air embolism.

INTERCHANGEABLE PROBES

The P81 probe is one of a family of probes made for use with the MedSonics VERSATONE® Doppler instruments. It is easily interchangeable with other probes manufactured for this instrument.

LISTED UL 178T

P82/P83

The Model P82 and P83 Doppler ultrasound pencil-shaped probes may be used transcutaneously to detect blood flow or intraoperatively to examine flow in vessels exposed during surgical procedures.

P84

The Model P84 probe is designed for use in monitoring blood flow on the principal blood vessels of the arms or legs. It is possible to take systolic blood pressures even in hypotensive patients in conjunction with a cuff and manometer.

FOR MORE INFORMATION CONTACT

MEDA SONICS

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Toll free telephone: 800 227-8076
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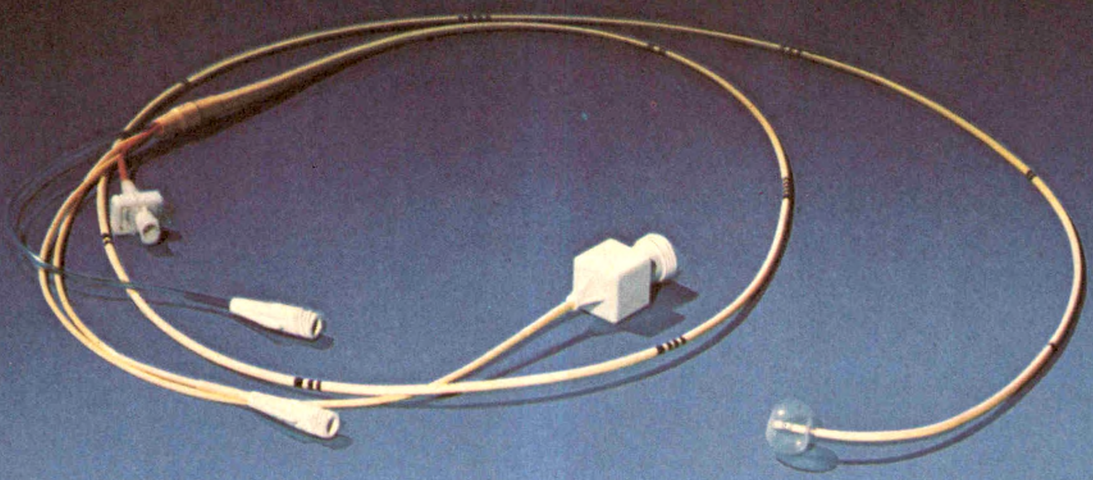


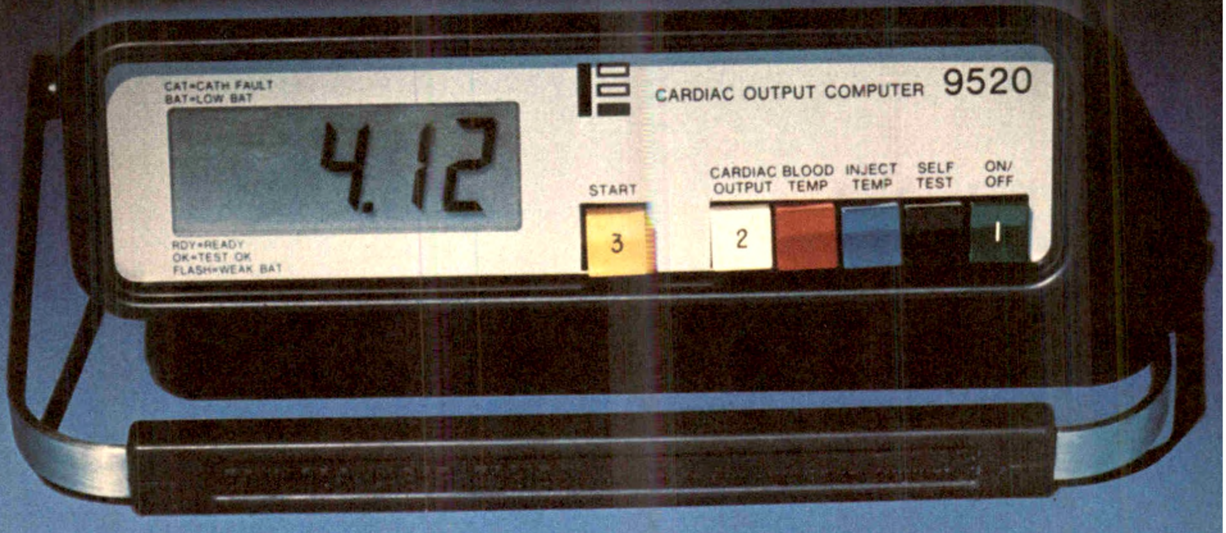
One good idea

The SWAN-GANZ®

The SWAN-GANZ Flow-Directed Catheter was the original idea and is now the most widely used catheter of its kind in the world. The Edwards Cardiac Output Computer was also a first. Now in its fourth generation, it is highly regarded for its simplicity of operation, state-of-the-art electronics, and compact, portable size. Each has been designed for the other, to assure system reliability and performance.

When you decide on a SWAN-GANZ Hemodynamic Monitoring System, you also decide on a company that is totally committed to the design, development and manufacture of biomedical devices used in cardiovascular and critical care medicine.

You get better service because we assume full-system responsibility. As new thermodilution catheter models are introduced, we make sure they are compatible with our existing computers, so your system never becomes obsolete. And we back our systems with comprehensive training, applications assistance, technical literature, and reprints of medical-journal papers by distinguished physicians.



leads to another.

Hemodynamic Monitoring System.

SWAN-GANZ Thermodilution Catheters are available in 2.5F, 5F, and 7F sizes for a wide range of patient applications. The catheters, plus the Edwards Model 9520 Cardiac Output Computer and accessories, comprise a complete system for determination of cardiac output.

So decide with confidence on the SWAN-GANZ Hemodynamic Monitoring System. Available only from Edwards Laboratories, the recognized leader.

Another good idea: Request our fact-filled literature package. Please phone or write: Edwards Laboratories, Division of American Hospital Supply Corporation, 17221 Red Hill Avenue (Irvine), P.O. Box 11150, Santa Ana, CA 92711. Phone: 714/557-8910. Cable Address: EDSLAB. Telex: 68-5567.

EDWARDS LABORATORIES®

Division of American Hospital Supply Corporation

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109089-1 Rev.N/C

Selected cases for Ketala

There are certain situations where the advantages of Ketalar suggest its serious consideration. Four such hypothetical situations are detailed here.
A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.

Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).

Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgical anesthesia (generally within three to four minutes) at a range of 9 to 13 mg/kg, with the effect lasting from 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burn patients (particularly helpful in children where the veins are small). IM administration is also convenient and effective for repeated short-term anesthesia for such procedures as changing burn dressings, and skin grafts.

advancement in anesthesiology
Ketalar
(Ketamine HCl injection)
Parke-Davis

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;
2. for the induction of anesthesia prior to the administration of other general anesthetic agents;
3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced p[illegible]ssor response.
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension

(ketamine HCl inj) . . . and a caution

Manipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must be moved freely, and in which the maintenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be transferred from a supine to an upright, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.

Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.

A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

---

and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

DOSAGE AND ADMINISTRATION

Preoperative Preparations:

1. While vomiting has been reported following Ketalar administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, since these reflexes may also be diminished by supplementary anesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketalar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.
2. Atropine, scopolamine, or other drying agent should be given at an appropriate interval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4581-12—Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4582-10—Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.

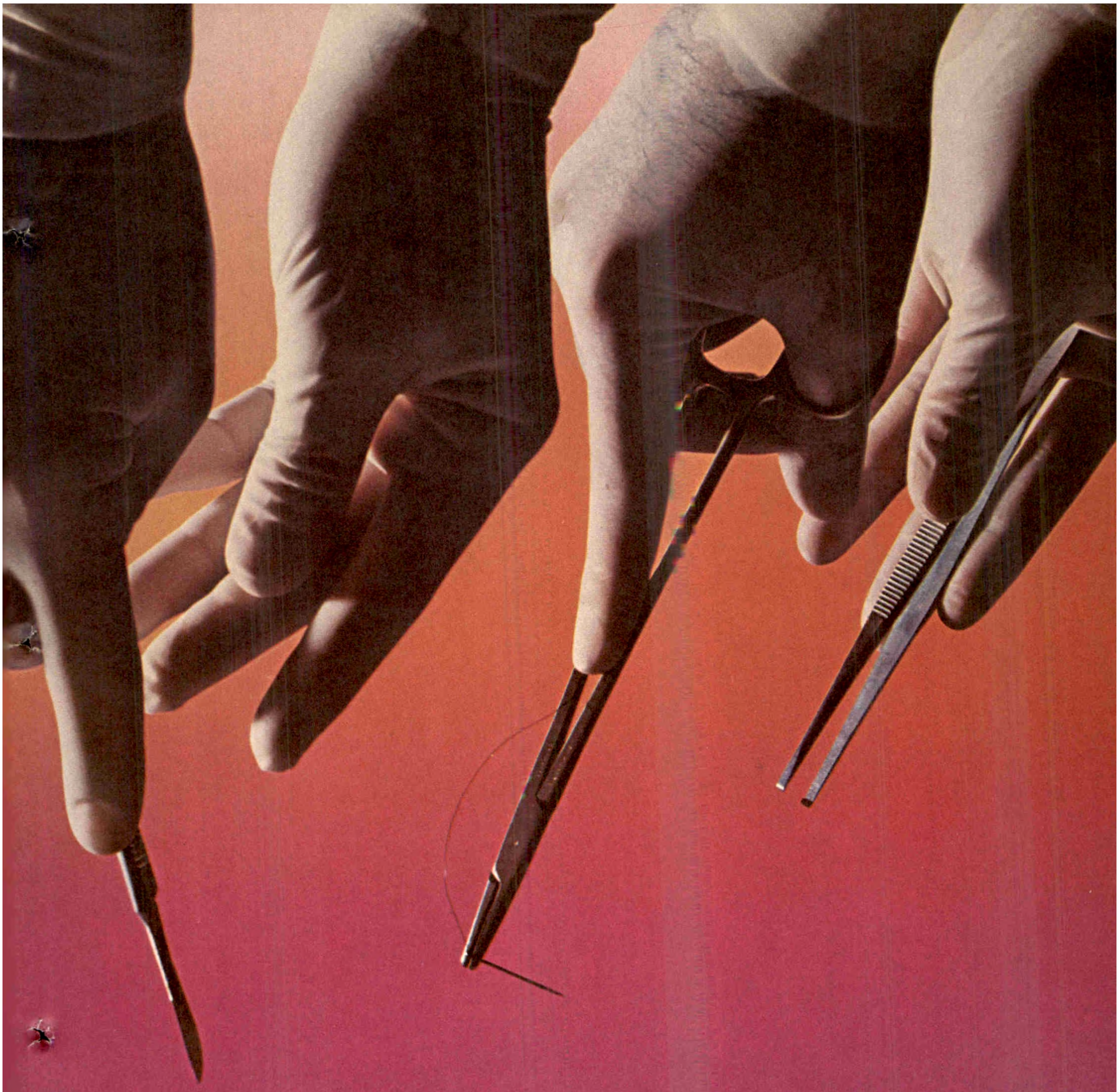
N 0071-4585-08—Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10. **SG**

PD-JA-1839-2-P (8-76)

PARKE-DAVIS

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950

Beginning with intubation,
Proceeding through surgery,
Until closure
Proceed with



Pavulon facilitates intubation and provides safe, neuromuscular blockade.

Histamine release and ganglionic blockade are rarely, if ever, seen[1]

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West Orange, N.J. 07052

PAVULON®

pancuronium bromide

For a brief summary of prescribing information, please see the following p

Until closure
Proceed with PAVULON®
pancuronium bromide
The clinically proven nondepolarizing muscle relaxant

Brief Summary (Please consult full package insert, enclosed in every package, before using Pavulon).

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

Reference:
1. Stanley and Liu, Anesth Analg 56:669, 1977

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MULTIPLE SCLEROSIS IS OF VITAL CONCERN TO EVERYONE WHO LIVES HERE.

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MS

National Multiple Sclerosis Society
257 Park Avenue South
New York, New York 10010

International Anesthesia Research Society

53rd Congress

March 11–15, 1979-Diplomat Hotel, Hollywood, Florida

MEETING SCHEDULE

Registration: Sunday, March 11–1 to 7 p.m.

Scientific Program: Monday, March 12–Wednesday, March 14–8:30–5:00

Thursday, March 15–8:30–12 p.m.

Concurrent sessions will be held throughout the 3½ day scientific meeting except for the Becton, Dickinson and Baxter/Travenol Lectures which will be given at single sessions on Monday and Tuesday afternoons. Review courses will be given on Wednesday afternoon and Thursday morning. A total of 58 scientific papers and 14 review courses will be offered in addition to the aforementioned Lectures.

PRELIMINARY PROGRAM
MEETING REGISTRATION AND HOTEL RESERVATION CARDS

These are available from the Cleveland office of the I.A.R.S.

FEES	**Paid by March 10**	**Paid at Meeting**
IARS Members	$40.00	$ 50.00
IARS Educational Members	NO FEE	NO FEE
Non-IARS Members	$75.00	$100.00

IARS members outside of the U.S. who plan to attend the meeting should advise Cleveland office promptly so that pre-registration material can be sent by air mail.

SCIENTIFIC AND TECHNICAL EXHIBITS

Individuals or institutions wishing to present scientific exhibits should request application forms from Cleveland business office. Commercial firms desiring exhibit space should contact Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, New Jersey 08086.

CONTINUING MEDICAL EDUCATION CREDIT

As an organization accredited for continuing medical education, the International Anesthesia Research Society certifies that the continuing medical education activities designated Category 1 meet the criteria for Category 1 on an hour-for-hour basis for the Physicians Recognition Award of the American Medical Association. (Note: An individual who takes full advantage of the scientific program can accumulate a maximum of 22 credit hours in Category 1.)

IARS 53rd CONGRESS DISTINGUISHED LECTURERS

Seventeenth Annual Baxter/Travenol Lecture

Monday, March 12–1:30 p.m.

"Cerebral Blood Flow: Importance for Neuroanesthesia and Intensive Care of Brain Injured Patients"

Niels A. Lassen, M.D.
Professor of Clinical Physiology

Bispebjerg Hospital,
Copenhagen, Denmark

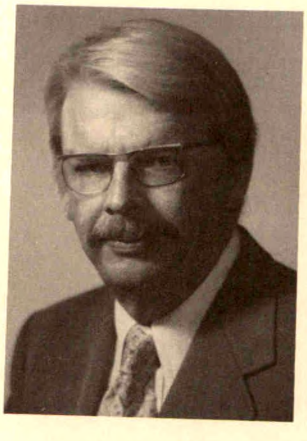
Fourteenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture

Tuesday, March 13–1:30 p.m.

"Adrenergic Receptors and Others"

Raymond P. Ahlquist, Ph.D.
Charbonnier Professor, Pharmacology

Medical College of Georgia
Augusta, Georgia



EDITORIALS

On Central Tendency and the Meaning of Mean for pH Values*

A SINGLE EXPRESSION is often used to summarize a set of data, so that a reader can get an idea of the "location" of the numbers without having to inspect the entire collection. An *index of central tendency* is the name given to the expression that serves this purpose; and three different statistical indexes are available: the mode, the median, and the mean.

Each of these indexes is determined in a different way. The *mode* is found by counting, since it represents the single item that occurs most frequently in the data. The *median* is found by ranking and counting, since it represents the middle value in the array formed when the individual items of data are arranged in ascending magnitude. The *mean* is the only summary index that requires arithmetic. It is calculated as an "average" of all of the items in the data.

Almost all investigators are aware of the distinctions just cited, but not everyone knows that an average can be calculated in at least four different ways. The decision about which way is best is the source of the current dispute about how to express the mean for a set of pH values.

The most common method of calculating a mean is used so often that most people regard it as the only kind of "mean." What it yields, however, is properly called an *arithmetic mean*: the sum of the items in the data, divided by the number of items. Thus, if a set of data contains the four values **31, 32, 33,** and **34,** the arithmetic mean is 130 ÷ 4 = 32.50. In mathematical symbols, the formula for the arithmetic mean is $\Sigma x_i/n$, where x_i is any one of the items, n is the number of items, and Σ represents the act of addition.

The second method, which produces a *harmonic mean,* is used so rarely that I cannot find a good medical example of its application. It is calculated by adding the *reciprocals* of the original values, getting the arithmetic mean of the reciprocals, and converting back to its reciprocal. In the cited set of data, the four values would have a harmonic mean of $1 \div \{[(1/31) + (1/32 + (1/33) + (1/34)] \div 4\} = 1 \div \{[.03236 + .03125 - .03030 + .02941] \div 4\} = 1 \div \{.12322 \div 4\} = 32.46$. In mathematical symbols, the formula is $n/\Sigma[1/x_i]$.

The third method, which is so esoteric that I discovered its existence only while preparing this editorial, produces what is called the *quadratic mean* or the *root mean square.* It is the square root of the arithmetic mean of the squared values. The mathematical expression is $\sqrt{\Sigma x_i^2/n}$; and for our illustrative data, the quadratic mean is $\sqrt{(31^2 + 32^2 + 33^2 + 34^2)/4} = \sqrt{4230/4} = 32.52$.

The fourth method, which is uncommon but not rare, produces the *geometric mean.* Here, we multiply the n items of data together and take their nth root. For the four cited values, the geometric mean is $(31 \times 32 \times 33 \times 34)^{1/4} = \sqrt[4]{1113024} = 32.48$. Using Π as the mathematical symbol for multiplication (analogous to the Σ used for addition), the formula is $(\Pi x_i)^{1/n}$. In the days before hand calculators were readily available to do things like taking nth roots, the simplest way to get the geometric mean was to work with the logarithm of each value, find the arithmetic mean of the sum of logarithm values, and take its antilog. Thus, with our illustrative data, we would first calculate the following: $(\log 31 + \log 32 + \log 33 + \log 34)/4 = (1.49136 + 1.50515 + 1.51851 + 1.53148)/4 = 1.51163$. The antilog of the arithmetic mean of the logs yields exactly the same value produced by the multiplicative formula for the geometric mean. Thus, $10^{1.51163} = 32.48$.

All of these different ways of calculating a mean may be interesting, but none of the mathematical strategies contains an answer to the primary question: what is the best way to represent the central tendency of a set of data? This question, alas, cannot be answered with any mathematical proof, since the answer depends on the intuition of the person examining the data. Although this intuition occurs differently to different people, most scientific workers would probably choose the median, rather than a calculated value, as the best index of central tendency. As the middle item in the ranked array of data, the median is the central point: half the items lie on one side of the median, and half on the other.

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* *The uncertainty surrounding the most appropriate method for calculation of mean pH values is exemplified by the Letter to the Editor from Drummond on page 63 of the present issue and by previous letters on the same subject from Krause (57:143–144, 1978) and from Giesecke et al (57:379–381)*—Editor.

The use of a median is often mathematically unappealing, however. Any one of the four kinds of means can be easily obtained by adding, multiplying, dividing, or doing other computations with a calculator, but (unless a special program is employed) the median requires the manual work of ranking and counting. For data expressed in measured dimensions, the median is found only after the individual items are laboriously arranged in rank order, and after the number of items is counted to note the middle one. Furthermore, if n is an even number, the median falls midway between the two middle items and is arbitrarily created by splitting the difference between them. (For example, in the cited set of data, the median lies between 32 and 33 and is designated as 32.5.) Finally, the median does not lend itself to mathematical manipulation in the elegant formulas used for various statistical tests of significance.

For all these reasons, despite the median's desirability, it has not become a popular index of central tendency. Since most investigators want an index that can be calculated, what we would prefer for central tendency is a calculated mean that comes close to being a median.

In the set of four values that have been used as illustrative data, any one of the four calculated means (32.50, 32.46, 32.52, and 32.48) is satisfactory, since each one is quite close to the median value of 32.5. Problems arise, however, when the individual values in a set of data extend through a large range. Suppose our four items were **3, 30, 300,** and **3000.** What is the best way to summarize the central tendency of this set of data? Simply looking at the data, without any other mathematical considerations, we would probably say that the best index of their central tendency is a value somewhere between the two middle terms, 30 and 300. Splitting the difference would give us 165, which is the median value.

When these four items are subjected to the calculations that yield the four kinds of means, the following results emerge:

Arithmetic mean = 833.25
Harmonic mean = 10.80
Quadratic mean = 1507.56
Geometric mean = 94.87

Of these four calculated means, the geometric mean is the only one that falls in the acceptable zone (between 30 and 300) and that comes even close to the median of 165.

This feature of the geometric mean—its likelihood of providing a central tendency that approximates the median—makes it particularly attractive as a way of summarizing data that span a very wide range. The geometric mean is thus the best way of citing the central tendency for such data as bacterial counts, antibody titers, or other information in which the basic measurements get their wide range by being expressed in powers of 10 (such as 5.1×10^2, 6.8×10^3, etc.) or in powers of some other number.

With this background, we can now turn to the problem of pH. The expressions for pH are derived from a power-of-ten measurement. As the logarithm of the reciprocal of the hydrogen ion concentration, pH is $1/\log[H^+]$ or $-\log[H^+]$. To go back and forth from pH to hydrogen concentrations, we can use the formula $[H^+] = 10^{-pH}$. Thus, if the pH is 7.45, the hydrogen ion concentration is $10^{-7.45} = 3.55 \times 10^{-8}$. If $[H^+]$ is 3.16×10^{-5}, pH is $(-5) + \log 3.16 = -5 + .5 = 4.5$.

Now suppose we have a set of pH data containing the values of **1.5, 3.6, 6.7,** and **8.9.** The respective $[H^+]$ values will be $.3162 \times 10^{-1}$, $.2512 \times 10^{-3}$, $.1995 \times 10^{-6}$, and $.1259 \times 10^{-8}$. This large range of variations in $[H^+]$ will not have its central tendency well expressed with the arithmetic mean. Adding the H^+ concentrations will lead to an arithmetic mean of $.0797 \times 10^{-1}$, which yields a pH of 2.10—a poor representation of central tendency in the cited data. On the other hand, suppose we take the geometric mean of the four hydrogen ion concentrations. This mean is $[(.3162 \times 10^{-1}) \times (.2512 \times 10^{-3}) \times (.1995 \times 10^{-6}) \times (.1259 \times 10^{-8})]^{1/4} = [.001995 \times 10^{-18}]^{1/4} = [.1995 \times 10^{-20}]^{1/4} = .6683 \times 10^{-5}$. The pH of this geometric mean for $[H^+]$ is 5.18, a much better indicator of central tendency for the data, particularly since it is close to the median pH value of 5.15, which is $(3.6 + 6.7)/2$.

Now suppose we had found the mean pH simply by taking the arithmetic mean of the pH values. This mean is $(1.5 + 3.6 + 6.7 + 8.9)/4 = 20.70/4 = 5.18$, a result that is identical with what was obtained with the geometric mean of the $[H^+]$ values. Thus, the arithmetic mean of the pH values yields the same result that would be obtained by getting the geometric mean of the hydrogen ion concentrations, and converting it to a pH value.

Consequently, the answer to the question about how best to calculate the mean of a set of pH values is simple. Deal with the values directly, and determine their arithmetic mean. It will produce exactly the same result one would get from the optimal way, i.e. the geometric mean, of managing the data expressed in hydrogen ion concentrations.

Before concluding this commentary, I thought it might be interesting to check for observer variability among statistical consultants. I therefore telephoned Professor John W. Tukey, who had been a chemist before becoming one of the world's leading statistical authorities on data analysis. Tukey's response to the question was immediate, "Take the arithmetic mean of the pH values." His rationale, however, was considerably more ingenious than the one I have offered. Instead of referring the pH values to hydrogen ion concentrations, developing the geometric mean for the $[H^+]$ data, and converting that mean to a pH value, Tukey makes matters much more simple. Since pH is what will determine electrode potentials and other chemical potentials, Tukey suggests that pH is chemically the main entity to be considered and the hydrogen ion concentration is essentially a derivative transformation, representing the negative exponential of the pH. Thus, in Tukey's view, the "primary" measurement is the pH; and the "secondary" scale of measurement is $[H^+] = 10^{-pH}$. Since pH does not have a wide range of values, its mean can be calculated with the standard additive procedure.

Regardless of whether you prefer Tukey's rationale or mine the recommendation is the same: add the pH's and divide by n to get their mean.

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On Knowing Your Own History

GREENE'S paper in the current issue on the relationship between the introduction of anesthesia and the development of surgery raises a major question: "Why did it take so long for ether anesthesia to have a discernible impact on surgery after its demonstration in Boston in 1846?"

The distinguished author cites a number of possible reasons but perhaps a few more can be added. The successful use of ether by a Harvard medical student, William Thomas Green Morton—who had already qualified in dentistry—was revolutionary, in a reputedly conservative city.

Who was the surgeon? None other than the 70-year-old John Collins Warren, Professor and pioneer. As a young man Warren had studied with John Elliotson at the University College Hospital in London. Both were interested in the relief of pain and had turned to the study of hypnosis to see what it offered, if anything, by way of relief of suffering during surgery.

Thus, on October 16, a date that has subsequently come to be known as Ether Day, two pioneers, one young and one old, brought their hopes and their talents together in 1846 to make what has probably been America's greatest contribution to medicine. Its only rival for that title, as William Welch of Johns Hopkins used to say. was John Shaw Billings' development of the *Index Medicus*, or its forerunner, the *Index Catalogue of the Surgeon General's Library* in Washington. One of its worthy offspring, Medline, is well known to us in this computer age.

There is no need further to chronicle here the medical student contribution to the discovery and early use of anesthetic agents. It is all set out in *Young Endeavour*,* the most frequently stolen book in medical libraries, according to Yale's John Fulton.

What does it all mean? To those who have ears to hear, it signals the fact, so clearly documented in Greene's paper, that anesthetists have often been in the vanguard, well ahead of their surgical and obstetrical colleagues. They are particularly well equipped to chronicle the regrettable lag that often takes place between a discovery and its application.

The Greene paper is but the tip of an iceberg. The iceberg is this—what disease conditions filled our hospital beds in the respective centuries since, say, the year 1600? I was recently glancing over a small Rocky Mountain hospital admissions book, dating from 1890. There was clearly a race between alcoholism and typhoid in that community. Only typhoid could be said today to have vanished there.

Before it is too late, could not the anesthetists of the continent bring together the records of early anesthesia and surgery in their respective hospitals? Then we would have a vast treasure of information about a medical advance which began on a special day in 1846. Few things in medicine can be so exactly dated.

Anesthetists lack the self-confidence found in older specialties when it comes to putting together the history of their craft. I hope that Professor Greene's paper in the present issue will cause the men and women dedicated to this Cinderella of science to bring forth its noble and interesting history in the way which it clearly merits.

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* *W. C. Gibson: Young Endeavour: Contributions to Science by Medical Students of the Past Four Centuries. Springfield, Illinois, Charles C Thomas, Co., 1958.*

ANESTH ANALG
58:5-12, 1979

Anesthesia and the Development of Surgery (1846–1896)

Nicholas M. Greene, MD*

GREENE, N. M.: Anesthesia and the development of surgery (1846–1896). Anesth Analg 58: 5–12, 1979.

The hypothesis that the introduction of anesthesia in 1846 accelerated the development of surgery was tested by compiling statistics on the types of operations performed in this country and abroad in the absence of anesthesia (prior to 1846) and over the 50-year period after 1846. Prior to 1846, surgery involved the extremities and superficial parts of the body almost exclusively. The same was generally true for 50 years following 1846. The introduction of anesthesia was necessary before surgery could advance, but control of infection, establishment of the sciences of pathology and physiology, and development of professionalism in clinical medicine and surgery based on research and teaching were also required. Almost a half-century lapsed after the introduction of anesthesia before surgery advanced significantly beyond the stage it was at prior to the introduction of anesthesia in 1846.

Key Words: HISTORY: anesthesia; HISTORY: surgery.

SURGICAL anesthesia, one of the most humane discoveries in history, was introduced in 1846. Anesthetics were known before this time. The numbing effects of cocaine were recognized and indeed used by South American Indians before the arrival of the Spaniards terminated such an effective if primitive means for the control of pain. Nitrous oxide had been isolated in 1772 and its analgesic effects noted in 1800,[1] but its potential was not to be exploited for another 60 years. Ether was in wide use in medicine as a stomachic and general tonic prior to 1846,[2] but its anesthetic potential remained unrecognized. Even after Dr. Crawford Long first used ether to produce surgical anesthesia in Jefferson, Georgia, in 1842, the rest of the world remained ignorant of this remarkable discovery because Long never publicized his accomplishment. In retrospect it is perhaps almost predictable that anesthesia was not introduced prior to the middle of the 19th century.[3] Attitudes towards suffering and disease were not yet ready for the introduction and acceptance of something as new and revolutionary as surgical anesthesia, nor had the technology required for the introduction and practical application of anesthesia been developed. It was, on the other hand, perhaps almost inevitable that anesthesia would be introduced by the 1840s for the technology was available and, above all, the anatomic basis of disease and organ function was recognized with subsequent appreciation of surgery as a major form of therapy. Anesthesia was finally introduced on October 16, 1846, when William Morton, a dentist from Hartford, Connecticut, demonstrated before a group of surgeons at the Massachusetts General Hospital that inhalation of ether produced a state of insensibility to the pain associated with surgery. Within weeks the entire civilized world became aware of Morton's demonstration. Anesthesia was not only discovered, it was introduced into medicine.

Despite the fact that anesthesia was not available prior to 1846, surgery was, nonetheless, being performed. Herbals, alcohol, opium, hypnosis, cold, and assorted other technics were intermittently employed before 1846 to relieve the pain of surgery, but they were too unpredictable and proved too dangerous to be widely accepted. Operations, terrible experiences for patient and surgeon alike, were accomplished

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mainly by holding or tying the patient down and getting the procedure over with in the shortest time possible.

In view of the horrors of surgery without anesthesia, to say nothing of the practical limitations inherent in attempting to operate on an unanesthetized patient, it might be assumed that lack of anesthesia inhibited the development of surgery prior to 1846. If so, then once anesthesia relieved surgery of the constraints placed upon it by pain, the practice of surgery would be expected to expand. The frequency of operations would be expected to increase, as would the types of varieties of operations performed. This is widely believed to be what happened, a school of thought exemplified by the statement of Comroe and Dripps in their article on the nature of biomedical discoveries to the effect that "When general anesthesia was first put to use in 1846, the practice of surgery exploded in many directions."[4] A contrary school of thought suggests that surgery did not change significantly in the years following the introduction of anesthesia because additional problems other than control of pain remained to be solved before modern surgery could develop. Neither position has been backed by quantitative data adequate to prove the extent to which the introduction of anesthesia may or may not have affected the development of surgery.

The present study attempts to quantitate the relationship between the introduction of anesthesia and the development of surgery by examination of surgical records available prior to 1846 and comparing them to records available during the 50 years thereafter. Types of operations, not frequency of operations, are relied upon as a reflection of the state of the art of surgery during the period studied. Attempts to determine the frequency of operations in terms of procedures per 100,000 population were abandoned as an index of the state of surgery since the populations served by those few hospitals which maintained accurate surgical statistics could not be readily determined. Furthermore, throughout much of the 19th century substantial numbers of operations were performed outside of hospitals, especially in homes. Data on the frequency or types of domiciliary surgery are totally lacking. The assumption that hospital operative statistics constitute an accurate index of the types of operations being performed appears reasonable. It seems unlikely that new, innovative surgical technics would be carried out only in homes and not in hospitals. It seems more probable that new operative procedures would be introduced first in hospitals and would continue to be performed in hospitals while also perhaps constituting a portion of domiciliary surgery.

Material and Methods

A large number of "hospitals" were in existence in the United States prior to 1846. The majority were institutions for the insane or were little more than almshouses. In this country prior to 1846 there were only six acute, general care hospitals in which surgical operations were routinely performed: Massachusetts General Hospital, New Haven Hospital, New York Hospital, Bellevue Hospital, Pennsylvania Hospital, and Philadelphia General Hospital. The records of these six hospitals were examined insofar as they were available prior to 1846 to determine the types of operations being performed. The resulting data were then compared to similar data from the same institutions as well as from other hospitals between 1846 and 1896.

In several of the six United States hospitals in existence prior to the introduction of anesthesia there are no records of any type available prior to 1846. In others, records that are available deal with material of considerable interest from other points of view but are of little value insofar as they shed light on what constituted the practice of surgery in the years involved. There are records of selected operations, the Surgical Register of the New York Hospital for the years 1808 to 1833, for example. This Register consists primarily of accounts of interesting, spectacular cases. It is not a statistical enumeration adequate to permit quantitation of the types of operations performed. Annual reports of departments of surgery apparently were not made in United States hospitals prior to 1846. If reports were made, they were not incorporated into the permanent records of the institutions. Annual statistical tabulations of operations performed were not to become routine until the 1860s.

The one exception to the general dearth of reliable surgical statistics in United States hospitals prior to 1860, especially prior to the introduction of anesthesia in 1846, is the "Analytic Index of Surgical Records of the Massachusetts General Hospital from its Foundation in 1821 to 1866," a compilation later extended to 1870. A hand-written ledger prepared by Samuel Kneeland, Jr., M.D., the Index lists presumably all operations performed at the Massachusetts General Hospital over a period of 49 years. This Index proved to be the only source of statistical data available for quantitation of the types of surgery routinely performed in this country prior to 1846 and in the years immediately thereafter.

The paucity of surgical statistics in the United States prior to 1860 and, especially important, prior to 1846, stands in contrast to data that are available from Scotland and from London for the same period. Here one finds lists of operations which are clear, complete, and systematic. The British lists closely resemble those found in the Massachusetts General Hospital Index. Together, these sources of surgical statistics are assumed to reflect the state of surgery in the Western world prior to the introduction of anesthesia, as well as in the years between 1846 and 1860 when reporting of surgical statistics became routine and commonplace. Records from additional hospitals in this country and from hospitals in Great Britain were used to supplement data from the Massachusetts General Hospital as records became more generally available in the years following the Civil War.

Standard nomenclatures of diseases and operations did not exist in the 19th century. Indeed, within the same hospital, classification and descriptions of operations frequently varied from year to year. In the absence of systematic and consistent methods for recording operative procedures, it was considered more appropriate to list operations exactly as they were reported instead of attempting to rearrange them according to currently accepted standard nomenclature. The disadvantage of the resulting, perhaps unfortunate, number of tables was compensated for by the preservation of accuracy.

Results

The types of surgery performed at the Royal Infirmary of Edinburgh during 1839–1843 are summarized in Table 1.[5-7] In this and in subsequent data, up to about 1890, "hernia" operation refers to herniotomy, not herniorrhaphy. Lithotrity consisted of crushing of a stone, usually in the bladder, and usually accomplished transurethrally. Lithotomy refers to removal of a stone, usually in the urinary bladder, through a perineal or suprapubic incision, although occasionally the transrectal approach was used. Notable is the preponderance of operations that were superficial. Many were on the extremities.

The Royal Infirmary of Edinburgh was a major teaching-university hospital in the 1840s, but the same types of surgery were being performed elsewhere in Scotland (Table 2).[8] Data from Guy's Hospital in

TABLE 2
Operations Performed in Eight Civil Hospitals in Scotland in 1844

Amputations	154	Tracheotomy	5
Cleft palate	1	Fistula in ano	20
Cataract	17	Harelip	7
Exc. elbow joint	5	Hernia	11
Exc. malignant tumors:		Hydrocele paracentesis	20
upper jaw	2	Lithotomy	28
lip	15	Laryngotomy	1
cheek	2	Lig. arteries	5
neck	2	Perineal cystotomy	2
breast	17	Paracentesis ascitis	4
other	5	Exc. testicle	2
Exc. nonmalignant tumors	18	Strabismus	1
Exc. tonsils	2	Tenotomy	9
Exc. hemorrhoids	1	Trephine	3
Exc. "other parts"	33	Miscellaneous	16
		Total	408

TABLE 1
Operations Performed at Royal Infirmary of Edinburgh

1839–1841		1841–1842		1842–1843	
Amputations, extremities	69	Amputations of extremities	38	Amputations of extremities	16
Exc. lesions from various parts*	43	Exc. portion of lower jaw	1	Exc. upper jaw	2
Exc. bony structures	10	Exc. elbow joint	3	Exc. eyeball	1
Castration	2	Trephine	2	Exc. elbow joint	1
Lithotomy and lithotrity	7	Exc. eyeball	1	Exc. tumors in various parts	21
Ligation arteries	8	Exc. tumors of breast	7	Ligation arteries	2
Hernia	6	Exc. tumors of other parts	29	Lithotomy	1
Harelip	8	Restoration of nose	2	Exc. testicle	1
Removal of portions of bones	12	Harelip	1	Harelip	2
Div. tendons for clubfoot	12	Tracheotomy	4	Total	47
Div. of other tendons	4	Hernia	4		
Restoration nose and lower lip	2	Lithotomy	4		
Lachrymal fistula	3	Removal of testicle	1		
Tracheotomy	6	Amputation, penis	1		
Total	192	Ligation femoral artery	4		
		Exc. os calcis	2		
		Total	104		

* Scalp, jaw, face, head, shoulder, neck, back, eyelid, orbit, throat, axilla, penis, vulva.

London (Table 3)[9-12] are closely similar to those reported from Scotland. Table 3 also includes operations performed in the first few months following the introduction of anesthesia in London, some 3 weeks after Morton's demonstration in Boston. With the single exception of one operation for ovariotomy at Guy's Hospital in 1843, surgery was also characteristically superficial. Theoretically, intraabdominal procedures (Tables 1 to 3) might have been included as "miscellaneous" procedures. This seems unlikely. An intraabdominal operation would have been notable enough to warrant a separate heading, especially when each harelip and each castration is so carefully documented. Gastrectomies or splenectomies are not likely to be hidden under the heading of miscellaneous operations.

Essentially the same type of surgery was being performed in Boston prior to 1846 (Table 4). Noteworthy is the fact that hernia operations do not appear in Table 4. Perhaps this is because they were recorded under a different heading and are thus disguised, or perhaps hernias were not being operated upon as frequently in Boston as they were in Britain. Other records from the Massachusetts General Hospital indicate that patients with hernias were being admitted to the hospital at this time. Apparently they were not treated surgically.

Statistics such as those in Tables 1 to 4 indicate that surgery was being performed prior to the introduction of anesthesia but that it was almost exclusively superficial in nature. What happened after 1846? Table 5 reveals that in 1853, 7 years after anesthesia became available, the type of surgery performed at Guy's Hospital[13] had changed little, if at all. Surgery remained primarily superficial. The types of operations performed were essentially the same as they were prior to 1846. Perhaps this was because the English were too conservative to expand the frontiers of their surgery in but 7 years. Data from the General Hospital of Madrid[14] were, however, similar (Table 6). Indeed, the situation remained essentially unchanged until the 1860s. Between 1861 and 1868 operations at Guy's Hospital[15] were still predominately superficial in nature (Table 7). For the first time, however, intraabdominal procedures were recorded: two splenecto-

TABLE 3
Operations Performed at Guy's Hospital, London

	Jan. 1, 1843–Dec. 31, 1843	Jan. 1, 1844–Dec. 31, 1844	Jan. 1, 1845–Mar. 31, 1846	Apr. 1, 1846–Mar. 31, 1847
Amputations	24	23	34	30
Hernia	3	7	11	18
Lithotomy	7	13	18	4
Lithotrity	2	2	3	2
Ligation arteries	2	3	2	3
Trephine	4	3	1	—
Exc. tumors	24	24	41	12
Castration	—	1	1	1
Exc. bone or cartilage	—	2	3	4
Harelip	1	1	—	—
Exc. breast	—	—	—	9
Ovariotomy	1	—	—	—
Tracheotomy	—	—	2	—
Cleft palate	1	—	—	—
Miscellaneous	4	12	22	18
Total	73	91	138	101

TABLE 4
Operations Performed at Massachusetts General Hospital, 1821–1846*

Amputations, extremities	123
Amputations, penis	4
Aneurysm	15
Ligation arteries	17
Urinary bladder operations	17
Cancer of	
breast	62
face	2
nose	1
head and neck	1
lower lip	22
penis	4
leg and thigh	3
tongue, mouth, and upper lip	9
Castration	33
Clubfoot	20
Total	333

* Excluding (1) puncture, incision or drainage of abscesses; (2) fissures and fistulae in ano; hemorrhoidectomy.

TABLE 5
Operations Performed at Guy's Hospital, April 1, 1853–Sept. 30, 1853

Amputation	25
Hernia	9
Oper. on bones of head	3
Lithotomy	9
Lithotrity	2
Incision perineum	4
Exc. necrotic bone	15
Exc. elbow	2
Lig. arteries	2
Exc. tumors	40
Laryngotomy	1
Division sphincter	11
Miscellaneous	12
Total	135

TABLE 6
Operations Performed at General Hospital of Madrid, Jan. 1, 1853–Dec. 31, 1853

Amputation	29
Circumcision	2
Exc. stricture urethra	1
Plastic oper. on eye	1
Exc. head of humerus	1
Esc. wens, warts	3
Exc. hemorrhoids	3
Exc. cancer lip	2
Exc. tumors	10
Fistula in ano	4
Puncture of hydrocele	4
Miscellaneous	7
Total	67

TABLE 7
Operations Performed at Guy's Hospital, 1861–1868

Amputations of limbs	305	Oper. on blood vessels	41
Exc. tumors:			
breast	147	Plastic operations	114
cancerous	75	Urethral operations	65
fibrous, fibroid and encysted	91	Transrectal cystotomy	30
cartilaginous	19	Lithotomy, lithotrity	122
vascular and nevus	14	Trephine	51
fatty	50	Pharyngotomy	1
glandular	8	Laryngotomy	2
Exc. diseased joints	13	Tracheotomy	65
Exc. diseased bones	234	Abd. section for deformed pelvis	2
Exc. spleen	2	Cesarean section	1
Exc. "end of stump"	14	Gastrotomy	1
Exc. penis	24	Colotomy	4
Exc. testicle	35	Ovariotomy	44
Exc. tongue	1	Hernia	152
		Total	1667

mies; two abdominal sections for deformed pelvis (perhaps cesarean sections, although unlikely since cesarean section is listed separately); one gastrotomy; four colotomies; and 44 ovariotomies. But a total of only 54 intraabdominal operations were performed over a period of 8 years, fewer than seven per year, and only 54 such procedures out of a total of 1667 operations. The bulk of surgery remained superficial and peripheral. The same was true at the Massachusetts General Hospital from 1847–1870 (Table 8), except that no intraabdominal operations were recorded. The absence of intraabdominal procedures in Table 8 is probably not a result of oversight on the part of Dr. Kneeland or difficulty on the part of this reviewer in finding such operations in the Index. No intraabdominal operations were recorded at the New Haven Hospital (Table 9) in 1867, 1872, or 1875.[16–18]

TABLE 8
Operations Performed at Massachusetts General Hospital, 1847–1870*

Amputations, extremities	1098
Amputations, penis	12
Aneurysm	46
Ligation arteries	31
Urinary bladder operations	88
Cancer of	
breast	237†
face	5
nose	7
head and neck	4
lower lip	148
penis	7
leg and thigh	4
tongue, mouth, and upper lip	6
Castration	84
Clubfoot	147
Total	1924

* Excluding (1) puncture, incision, or drainage of abscesses; (2) fissures and fistulae in ano; hemorrhoidectomy.

† Including 233 excisions and 4 amputations.

None were recorded at the Boston City Hospital[19] as late as 1883–1884 (Table 10).

The practice of surgery was not immediately or radically altered by anesthesia. Gradual changes did occur, but they were not evident until well into the 1890s. There are many statistics to show how surgery began to change in the 1890s, not only at the Massachusetts General Hospital, at Guy's Hospital, and at the Royal Infirmary of Edinburgh but in other institutions as well. By 1897, for example, operations performed at the New Haven Hospital[20] began to include intraabdominal interventions (Table 11): 21 appendectomies; six herniorrhaphies; 12 exploratory laparotomies; five oophorectomies; three tubo-oophorectomies; and one cholecystotomy. The rate of change accelerated even more in the next decade. By 1910, Boston City Hospital[21] reported not only 606 intraabdominal procedures, but also 24 operations on the pleura and four operations on the respiratory tract other than on the pleura (Table 12). Statistics like these were becoming common amongst major university and city hospitals in the first decade of the 20th century. The ice had broken. Surgery was expanding its horizons.

Discussion

That surgery was being performed prior to the introduction of anesthesia is well recognized.[22] Lacking, however, as far as we can determine, are statistical data to quantitate the types of surgery being performed before ether and chloroform were used. The

TABLE 9
Operations Performed at New Haven Hospital

1867		1872		1875			
Amputations	3	Amputations	4	Amputations	7	Oper. for "necrosis"	3
Fistula in ano	3	Oper. on eye	1	Canthoplasty	1	Hemorrhoids	1
Exc. maxilla	2	Oper. on palate	1	Exc. bones	4	Paracentesis	2
Exc. testicle	2	Oper. on urethra	1	Iridectomy	3	Perineal section	1
Suprapubic cystotomy	1	Total	7	Lithotrity	5	Red. dislocation	2
Cancer breast	1			Cataract	5	Tenotomy	3
Tumor breast	1			Fistula in ano	2	Exc. tumors	9
Fissure of anus	1			Oper. on patella	1	Exc. sebaceous cysts	6
Total	14			Hydrocele	6	Miscellaneous	1
						Total	62

TABLE 10
Operations Performed at Boston City Hospital, 1883–1884

Amputations	64	Harelip	4
Aspiration, knee	3	Cleft palate	3
Abdominal tumor*	1	Exc. scars	3
Castration	6	Rectal oper.	55
Circumcision	16	Red. dislocations	22
Exc. toenail	12	Sequestrotomy	11
Rem. foreign bodies	7	Tenotomy	5
Hernia	10	Tracheostomy	46
Hydrocele	13	Trephine	4
I & D abscess	187	Exc. tumors	67
Ligation artery	4	Urethral oper.†	50
Lithotomy	5	Miscellaneous	6
		Total	604

* Patient died of "exhaustion."
† Includes 21 "rapid dilations."

TABLE 11
Operations Performed at New Haven Hospital, 1897

Amputation cervix	3	Exc. thyroid for goiter	1
Amputation extremities	25	Exc. tumor breast	6
Appendectomy	21	Gastrostomy	1
Bassini's oper.	3	Hysterectomy	2
"Radical cure" for inguinal hernia	3	I & D pelvis/abdomen	9
Enucleation eye	5	I & D other abscesses	8
Cataract	9	Oophorectomy	5
Sequestrectomy	18	Perineorrhaphy	11
Exc. carcinoma breast	10	Resection gut for carcinoma	1
Tenotomy	2	Skin grafting	1
Cholecystotomy	1	Trachelorrhaphy	4
Hemorrhoidectomy	10	Tracheotomy	1
Expl. celiotomy	12	Trephine	1
Curetting uterus	6	Tubo-oophorectomy	3
Exc. cancer mouth, jaw	8	Vag. hysterectomy	2
		Miscellaneous fractures, superf. tumors, etc.	91
		Total	283

TABLE 12
Operations Performed at Boston City Hospital, 1910

Dressing of wounds	25	Oper. on urinary system		101
I & D abscesses	388	Oper. on genitalia		54
Exc. tissue	67	Hernia		190
Oper. on skin	6	Plastic oper.		31
Fractures	100	Oper. on tumors without abd. section		48
Correction bony deformities	37	Foreign bodies		35
Trephine	13	Abd. section		606
Amputations	69	Exploratory	41	
Oper. joints, ligaments, and tendons	80	Stomach	23	
Oper. blood vessels	32	Small int.	17	
Oper. lymphatic system	62	Colon	14	
Oper. nervous system	7	Appendix	415	
Oper. rectum	38	Gall bladder	42	
Fistula in ano	37	Pancreas	1	
Hemorrhoids	68	Spleen	1	
Oper. alimentary system without abd. section	22	Uterus	37	
Oper. on thyroid	3	Peritonitis	15	
Oper. on pleura	24	Miscellaneous		5
Other oper. on resp. tract	7	Total		2155

present material provides such quantitation not only for the years prior to 1846 but also for subsequent years. The latter indicate that the types of surgery being performed were not significantly different during the years immediately after 1846. The conclusion is that anesthesia had minimal effects on the types of operations performed for many years, almost a half-century, after anesthesia became available. Since the types of operations performed are a reflection of the state of the art of surgery, it is concluded that the introduction of anesthesia had little immediate effect on the development of surgery.

The conclusion that anesthesia had little appreciable effect on the practice of surgery for a half-century after its introduction is based upon data reported from major hospitals in the United States and the British Isles. Whether a similar picture existed in Europe, especially in Austria and what is Germany today, is the subject of further investigation It is unlikely, however, that development of surgery in the United Kingdom lagged behind that on the Continent. For much of the period between 1846 to 1896 surgery in the great Scottish and English universities was more advanced than it was in most European universities. The ascendency of surgery in German-speaking Europe did not start until the mid-1880s and did not reach its peak until the mid-1890s That surgery in the United States lagged behind surgery in England and Scotland is, however, suggested by the observation that intraabdominal operations were not recorded in the United States for at least two decades after they were being reported in Britain (Tables 7 to 9).

The conclusion of the present study is based upon the types of operations actually performed in the everyday practice of surgery in hospitals in the United States and Great Britain. New and innovative operations were certainly described for the first time in the period of 1846 to 1896, but for the most part they were daring, first-time procedures and as such were curiosities, not representative of standard forms of surgical management. The first nephrostomy was described in Hippocratic times, the first pneumonectomy in the 17th century, but neither nephrostomy nor pneumonectomy were routine procedures by the end of the 19th century. The first gastrectomy and the first colectomy were reported prior to 1895, but neither had become recognized standard procedures in wide use prior to 1895.

Why did anesthesia have so little immediate effect on the development of surgery? The introduction of anesthesia was, of course, essential for the development of surgery. Without anesthesia, surgery could not advance. Anesthesia, however, was but one of several ingredients needed before surgery could advance beyond the stage of treatment of superficial and peripheral pathology. Another necessary ingredient was the ability to control infection. This required first the discoveries of Pasteur in the middle and latter parts of the 19th century, but even after Pasteur demonstrated the necessity for cleanliness, practical techniques still had to be developed to attain asepsis. The Listerian principle of antisepsis, when finally introduced, was not adequate to allow surgeons to open uninfected joints or body cavities with impunity.[23] To do so required that the concept of antisepsis evolve into asepsis, and that practical means for achieving asepsis be at hand. A third ingredient required for the growth of surgery was development of a storehouse of fundamental background knowledge of normal and abnormal functions of the body. Until medical science knew more about normal and abnormal organ function, that is, until physiology and pathology became sciences, surgery could not advance any more than it could in the absence of anesthesia and asepsis. This did not happen until the last decades of the 19th century. Until the function of the stomach was understood, for example, and the diseases affecting it were recognized, gastrectomies were not performed.

The fourth ingredient required before surgery could realize its full potential was development of a sense of professionalism in medicine as a whole and in surgery in particular. Professionalism is the quality present in individuals who have become experts in a field by virtue of advanced study, who use their expert knowledge for the generation of new information through research, and who pass their knowledge on to others by teaching.[24] Professionalism in medicine and surgery developed more slowly than in other fields. Professionalism was well established by the 19th century in several nonscientific areas, notably literature, law, and theology. Professionalism in nonmedical sciences also antedated the appearance of medical professionalism by several decades, especially in chemistry, physics, mathematics, and biology. When professionalism finally did spread into the medical sciences, it first appeared in bacteriology and pathology and, shortly thereafter, in biochemistry.

There were isolated instances of medical and surgical professionalism prior to the end of the 19th century. Examples can be found as early as Renaissance times, especially in Italy. These examples, however, were manifestations of individual intellects. Few and far between, they were not representative of prevailing attitudes in clinical medicine. It was not until the last decades of the 19th century that there appeared on the scene a cadre of physicians who possessed a true sense of professionalism. The reforms instituted at Harvard Medical School by Charles Eliot in the 1870s were evidence of the developing sense of professionalism in the United States. So, too, was the opening of the first American university hospital at the University of Michigan in 1869, as well as the opening of The Johns Hopkins University in 1876 and its medical school in 1893.

The development of modern surgery required more than the control of pain afforded by anesthesia. It also required the ability to control infection, better understanding of normal and abnormal organ function, and a spirit of professionalism based on teaching and research. Almost 50 years passed before these three essential attributes had developed to the point where surgery could take advantage of the blessings afforded by anesthesia. At this point surgery began its development into a scientific, innovative discipline.

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Sudden Death in Bundle-Branch Block

Two hundred fifty-seven patients with bifascicular and trifascicular conduction-system disease and intact atrioventricular conduction were followed prospectively. Forty-seven percent had associated coronary-artery disease, and 23% primary conduction-system disease. During an average follow-up period of 25 months, 50 patients died. However, death was sudden in only 27 cases, and 17 of the sudden deaths were not due to bradyarrhythmias. Actuarial analysis showed an overall mortality rate (mean ± SE) of 19 ± 2.6% at 2 years, mortality from sudden death being 10 ± 2.6%. Permanent heart block occurred in 12. No clinical symptoms (including syncope), electrocardiographic findings, electrophysiologic data, or their combination identified patients at high risk of sudden death. Sudden death due to bradyarrhythmia is uncommon in patients with bundle-branch block and intact atrioventricular conduction. Therefore, routine prophylactic use of permanent pacemakers in all such patients is inappropriate. Pacemaker implanation should be reserved for those with documented symptomatic bradyarrhythmias. *See Also*—Editorial. Kastor JA: Cardiac electrophysiology: hemiblocks and stopped hearts. N Engl J Med 299: 249–250, 1978. *(McAnulty JH, Shahbudin HR, Murphy ES, et al: A prospective study of sudden death in "high-risk" bundle-branch block. N Engl J Med 299: 209–215, 1978)*

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Rapid Volume Expansion in Patients with Interstitial Lung Diseases

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Rapid administration of intravascular volume expanders is often necessary during anesthesia. Significant controversy still exists on the relative values of different volume expanders. Fifteen hypoxemic patients (Pa_{O_2} <70 torr on room air) were studied preoperatively. They were randomized into three groups. One group received 1.5 ml/kg of 25% salt-poor human albumin, a second group, 7 ml/kg of fresh frozen plasma; a third group, 7 ml/kg of 0.9% NaCl in water (normal saline). The infusions were given intravenously and completed in 20 minutes. Changes in hemodynamic pressures and flows, blood chemistries, and oxygen uptake and transport variables were studied. It was concluded that fresh frozen plasma afforded the greatest increase in cardiac output and oxygen availability with the least increase in left ventricular stroke work. Colloid osmotic pressure was more significantly increased by fresh frozen plasma than by salt-poor human albumin. Normal saline caused both a decrease in oxygen availability and colloid osmotic pressure. Pulmonary venous admixture increased to some extent in all patients receiving fresh frozen plasma or normal saline. In three patients, this increase was very marked and accompanied by severe arterial hypoxemia.

Key Words: BLOOD, Volume: expansion; FLUID BALANCE: volume expansion; PROTEIN: albumin, salt poor; BLOOD, plasma.

MAINTENANCE of adequate intravascular volume is of fundamental importance during administration of anesthesia.[1] Critically ill or unstable patients require particular attention to avoid excessive, as well as inadequate, administration of volume expanders. Several authors have recommended prehydration with colloid or crystalloid solutions before surgery.[1, 2] Others however have concluded that rapid volume expansion may have detrimental effects on oxygen uptake and delivery, although such conclusions have mainly been based upon studies made on patients in shock.[3] Relatively large volumes of fluids are often administered immediately after the induction of anesthesia. We planned to determine the effects of different volume expanders on the hemodynamic variables, on blood chemistries, and on oxygen uptake and transport of 15 patients.

The study was restricted to patients with interstitial lung disease who were hypoxemic (Pa_{O_2} <70 torr while breathing room air). Such patients represent a unique group, since the nature of their lung pathology may limit their ability to clear the increased extravascular lung water that accompanies a rapid expansion of intravascular volume.[4] Possible detrimental effects of fluids normally administered during anesthesia seemed to be worth investigating.

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Material and Methods

Fifteen patients, eight men and seven women, ages 35 to 63 years (mean 48.3); were studied after informed consent had been obtained. They had no previous history of heart disease. They all had a preoperative Pa_{O_2} at rest while breathing room air of <70 torr. Hypoxemia was caused by interstitial pneumonia in six leukemic patients, previous use of the chemotherapeutic agent bleomycin in four patients, and chronic interstitial pulmonary diseases in four patients; the cause was undetermined in one patient. Patients were scheduled for open lung biopsy (11 cases), drainage of intrabdominal abscesses (two cases), or exploratory laparotomy (two cases).

After induction of anesthesia with sodium thiopental, 3 mg/kg intravenously, the patients received pancuronium bromide (0.06 mg/kg) intravenously. Morphine sulfate (0.3 mg/kg) was given intravenously before and immediately after induction in two equal doses. After induction, mechanical ventilation was instituted with a volume-cycled ventilator and oxygen-enriched air, with FI_{O_2} 0.40.

To minimize the development of ventilation/perfusion abnormalities, 5 cm H_2O of positive end-expiratory pressure were added and relatively large tidal volumes (12 ml/kg/breath) were used. In addition, patients were maintained in a semisitting position with the head of the bed elevated 40 degrees. These precautions were taken in an effort to minimize the increase in closing volume that occurs in the recumbent position, as well as paradoxical movements of the diaphragm described in paralyzed, supine, mechanically ventilated patients.[5] No inhalation anesthetic gases were used since they might have prevented hypoxic vasoconstriction and increased $\dot{Q}_A/\dot{Q}_T$.[6] Sedation was maintained with a continuous infusion of sodium thiopental at 3 mg/kg/hr. This agent was chosen for its minimal effect on the variables we were studying.[7]

A balloon-tipped flotation catheter was inserted percutaneously through a jugular or subclavian vein into the pulmonary artery. A catheter was placed in a radial artery, percutaneously or by cut-down. No other surgical manipulations were performed during the study. Patients were randomized into three groups: one group received 1.5 ml/kg of 25% SPHA (see Appendix) intravenously over 20 minutes; the second group, 7 ml/kg of FFP intravenously over 20 minutes; the third group, 7 ml/kg of NS intravenously over 20 minutes. Immediately before the beginning, immediately after the end of the infusion (0 minutes), and 20, 40, and 60 minutes after that the following variables were measured:

HR was recorded from the digital display of the ECG monitor (Abbott Medical Electronics, North Chicago, Illinois).

$\overline{BP}$, $\overline{RA}$, $\overline{PAP}$, and $\overline{PWCP}$ were obtained by digital readout from a pressure monitor (Abbott Medical Electronics). Body surface area was calculated from height and weight.[8]

CO was measured in triplicate by thermodilution (cardiac output computer 9520, Edwards Laboratories, Santa Ana, California). CI, TPRI, LVSWI, PVRI, and RVSWI were calculated with standard formulas.[9]

At each time interval, samples of blood were obtained from the radial artery and the pulmonary

ABBREVIATIONS

SPHA	Salt-poor human albumin
FFP	Fresh frozen plasma
NS	0.9% NaCl in water (normal saline)
$\overline{HR}$	Heart rate (beats per minute)
$\overline{BP}$	Mean systemic pressure (torr)
$\overline{RA}$	Mean right atrial pressure (torr)
$\overline{PAP}$	Mean pulmonary artery pressure (torr)
$\overline{PCWP}$	Mean pulmonary artery capillary wedge pressure (torr)
CI	Cardiac index (L/min/m^2)
SI	Stroke index (ml/m^2)
TPRI	Total peripheral resistances index (dynes/sec/cm^{-5}/m^2)
LVSWI	Left ventricular stroke work index (gm/m^2)
PVRI	Pulmonary vascular resistances index (dynes/sec/cm^{-5}/m^2)
RVSWI	Right ventricular stroke work index (gm/m^2)
Pa_{CO_2}	Arterial carbon dioxide tension (torr)
Pa_{O_2}	Arterial oxygen tension (torr)
$P\bar{v}_{O_2}$	Mixed venous oxygen tension (torr)
Sa_{O_2}	Oxygen saturation of arterial blood (%)
$S\bar{v}_{O_2}$	Oxygen saturation of mixed venous blood (%)
Hb	Hemoglobin (gm/dl)
PA_{O_2}	Alveolar oxygen tension (torr)
P_{BAR}	Barometric pressure (torr)
P_{H_2O}	Partial pressure of water vapor (torr)
FI_{O_2}	Fractional concentration of inspired oxygen
R	Respiratory quotient
$P(A\text{-}a)_{O_2}$	Alveolar arterial oxygen gradient (torr)
$C(a\text{-}v)_{O_2}$	Arterial-mixed venous oxygen content difference (ml/dl)
$\dot{V}_{O_2}$	Oxygen consumption (ml/min/m^2)
$\dot{Q}_A/\dot{Q}_T$	Pulmonary venous admixture (%)
O_2ER	Oxygen extraction rate
$\dot{C}O_2$	Oxygen delivery (ml/min/m^2)
K^+	Serum potassium (mEq/L)
Ca	Serum total calcium (mg/dl)
Ca^{++}	Serum ionized calcium (mEq/L)
COP	Colloid osmotic pressure (torr)
SA	Serum albumin (gr/dl)
SP	Serum total proteins (gr/dl)
SC	Serum citrate (mg/dl)

artery. pH, Pa_{CO_2}, Pa_{O_2}, and $P\bar{v}_{O_2}$ were measured with a blood gas analyzer (blood gas analyzer 175, Corning, Madfield, Massachusetts). Sa_{O_2}, $S\bar{v}_{O_2}$, and Hb were determined by spectrophotometry (Co-oxymeter 182, Instrumentation Laboratory, Inc., Lexington, Massachusetts). $P(A\text{-}a)_{O_2}$ was calculated after having obtained PA_{O_2} with the following formula: $PA_{O_2} = (P_{BAR} - P_{H_2O}) \times FI_{O_2} - Pa_{CO_2}(FI_{O_2} + 1 - FI_{O_2}/R))$. $C(a\text{-}v)_{O_2}$, $\dot{V}O_2$, CO_2, O_2ER, and $\dot{Q}_A/\dot{Q}_T$ were computed with standard formulas.[9] P_{50} was calculated as previously described.[10] All hemogasometric values were adjusted for a temperature of 37 C.

Blood chemistry, analyses were performed on blood samples obtained simultaneously with the blood gases. K^+ was determined with an ion selective electrode (SS30-Orion, Cambridge, Massachusetts). Ca^{++} was determined with an ion selective electrode (SS20-Orion). CA, SA, SP, and SC were measured by spectrophotometry. COP was measured by pressure difference through a semipermeable membrane (Weil oncometer IL 186—Instrumentation Laboratory, Inc.).

Albumin, total protein, citrate, and COP were measured in each unit of FFP and SPHA. COP of SPHA was measured after having diluted each sample of 25% SPHA to a 5% concentration with NS.

For each variable studied, changes from baseline values were analyzed for significance with Student's *t*-test for paired data. Differences between the three groups were analyzed with Student's *t*-test for unpaired data. Correlation and multiple correlation between variables were analyzed with Pearson's product-moment formula.[11]

A probability level $p \leq 0.01$ was considered statistically significant. When $0.10 \leq p \leq 0.01$, an indication of tendency was assumed to exist.

Results

The baseline values for all variables studied were comparable in the patients of each group. PVRI and RVSWI were at the higher levels of normal in all patients (Table). $\overline{\text{PAP}}$, $P(A\text{-}a)_{O_2}$, and $\dot{Q}_A/\dot{Q}_T$ were abnormally high and Pa_{O_2} low for an FI_{O_2} of 0.40 (Table). These findings were expected, considering that hypoxemia and interstitial lung disease were present in all patients studied. All other variables were within normal limits. After administration of the volume expanders, the following changes were recorded:

TABLE
Baseline Data in the Three Groups of Patients

	SPHA group	FFP group	NS group
RVSWI (gm/m^2)	16.5 ± 2.56	18.25 ± 3.18	19.3 ± 4.35
PVRI (dynes/sec/ cm^{-5}/m^2)	207.6 ± 26.12	212.94 ± 28.3	197.34 ± 16.14
Pa_{O_2} (torr)	86.6 ± 6.86	80.9 ± 7.3	79.3 ± 6.59
$P(A\text{-}a)_{O_2}$ (torr)	128.9 ± 15.1	152.0 ± 28.8	147.7 ± 20.8
$\dot{Q}_A/\dot{Q}_T$ (%)	22.0 ± 2.49	22.2 ± 2.83	21.1 ± 2.09

Heart Rate

There were no significant changes in heart rate.

Hemodynamic Pressure Variables (Figs 1 to 3)

$\overline{\text{RA}}$ and $\overline{\text{PAP}}$ increased initially, in the FFP and NS groups, to approximately 3.5 torr above baseline. The pressure readings returned to baseline in 20 to 40 minutes. $\overline{\text{BP}}$ and $\overline{\text{PCWP}}$ remained unchanged. The COP-$\overline{\text{PCWP}}$ difference decreased significantly in the NS group (4.51 ± 0.73 torr below baseline at 0 minutes; 2.52 ± 0.68 torr below baseline at 60 minutes). This variable was unchanged or increased in the SPHA and FFP groups.

Hemodynamic Flow Variables (Figs 1 to 3)

Cardiac index increased in all groups, but the increase was maximal and of longest duration in the FFP group (0.73 ± 0.18 $L/min/m^2$ at 0 minutes; 0.53 ± 0.19 $L/min/m^2$ at 60 minutes). In the NS group it was minimal and of shortest duration. At 20, 40, and 60 minutes CI was significantly higher in the FFP than in the NS group. Since HR was unchanged, SI behaved in a fashion similar to CI. LVSWI and RVSWI also increased maximally in the FFP group (11.19 ± 1.87 gm/m^2 at 0 minutes; 12.91 ± 1.93 gm/m^2 at 60 minutes for LVSWI). No clinically significant changes were noted for the other variables.

	Minutes after infusion			
	0	20	40	60
CI	↑	↑	↑	↑
LVSWI	↑	↑	↑	↑
SA	⇑	⇑	⇑	⇑
COP	↑	↑	⇔	⇔
PaO_2	↓	↓	↓	↓
Hb	↓	⇔	⇔	⇔

↑ Increase from baseline values ($0.1 > P > 0.01$)
⇑ Increase from baseline values ($P < 0.01$)
⇔ No change from baseline values
↓ Decrease from baseline values ($0.1 > P > 0.01$)
⇓ Decrease from baseline values ($P < 0.01$)

FIG 1. Variables significantly affected by SPHA infusion.

	Minutes after infusion			
	0	20	40	60
$\overline{RA}$	⇑	↑	↑	⇔
$\overline{PAP}$	⇑	↑	↑	↑
CI	⇑	⇑	⇑	⇑
LVSWI	⇑	⇑	⇑	⇑
Ca^{++}	⇓	↓	⇔	⇔
SA	⇑	⇑	⇑	⇑
COP	⇑	↑	↑	⇔
PaO_2	↓	↓	↓	↓
Hb	⇓	⇓	⇓	⇓
$\dot{V}O_2$	↑	↑	⇑	↑
$\dot{C}O_2$	⇑	⇑	⇑	↑

↑ Increase from baseline values ($0.1 > P > 0.01$)
⇑ Increase from baseline values ($P < 0.01$)
⇔ No change from baseline values
↓ Decrease from baseline values ($0.1 > P > 0.01$)
⇓ Decrease from baseline values ($P < 0.01$)

FIG 2. Variables significantly affected by FFP infusion.

	Minutes after infusion			
	0	20	40	60
$\overline{RA}$	⇑	⇔	⇔	⇔
$\overline{PAP}$	↑	↑	↑	⇔
$COP - \overline{PCWP}$	⇓	⇓	⇓	↓
CI	↑	⇔	⇔	⇔
LVSWI	⇑	↑	⇔	⇔
CA^{++}	⇓	↓	↓	↓
SA	⇓	↓	⇔	⇔
COP	⇓	⇓	⇓	⇓
PaO_2	↓	↓	↓	↓
Hb	⇓	↓	↓	↓
$\dot{C}O_2$	↓	↓	↓	↓

↑ Increase from baseline values ($0.1 > P > 0.01$)
⇑ Increase from baseline values ($P < 0.01$)
⇔ No change from baseline values
↓ Decrease from baseline values ($0.1 > P > 0.01$)
⇓ Decrease from baseline values ($P < 0.01$)

FIG 3. Variables significantly affected by NS infusion.

Blood Chemistries (Figs 1 to 3)

Ca^{++} decreased significantly in the FFP and NS groups. The lowest value was noted in the FFP group at 0 minutes (0.18 ± 0.04 mEq/L below baseline). SA increased significantly in the SPHA group (0.44 ± 0.03 gr/dl at 0 minutes). In the NS group instead, there was a decrease of 0.26 ± 0.06 gr/dl below baseline at 0 minutes.

COP increased significantly in the SPHA group and even more in the FFP group (0.7 ± 0.10 and 1.5 ± 0.38 torr, respectively, at 0 minutes) and decreased significantly in the NS group (2.7 ± 0.14 torr at 0 minutes). COP returned rapidly to values close to baseline at 20 minutes in the SPHA and FFP group, while it was still 1.9 ± 0.11 torr below baseline at 60 minutes in the NS group. The difference between the SPHA and FFP groups and the NS group was significant at 0, 20, and 40 minutes. Ca, SP, and K^+ had no clinically relevant changes. SC increased in all groups.

Blood Gases (Figs 1 to 3)

Values for pH and Pa_{CO_2} did not change in any group. Pa_{O_2} decreased in all groups. The lowest values were obtained in the FFP group (9.00 ± 2.14 torr below baseline at 0 minutes). Sa_{O_2} followed the changes of Pa_{O_2}. $P\bar{v}_{O_2}$ increased slightly in early observations in the SPHA and NS group, but was below baseline in all groups at 60 minutes. $S\bar{v}_{O_2}$ changed accordingly. P_{50} increased significantly in the SPHA and FFP groups (0.99 ± 0.38 and 0.86 ± 0.15 torr at 60 minutes, respectively).

Oxygen Uptake and Transport (Figs 1 to 3)

Hb decreased in all groups, as anticipated by the dilution effect. $\dot{V}_{O_2}$ increased in the FFP group (22.11 ± 4.25 ml/min/m^2 at 60 minutes) and decreased in the NS group (13.75 ± 3.81 ml/min/m^2 below baseline at 60 minutes).

$\dot{C}_{O_2}$ increased significantly in the FFP group (73.5 ± 17.8 ml/min/m^2 at 60 minutes) and decreased in the NS group (60.5 ± 11.3 ml/min/m^2 below baseline at 60 minutes). The difference between the FFP and NS groups was significant up to 60 minutes. $P(A-v)_{O_2}$ and $\dot{Q}_A/\dot{Q}_T$ generally increased with very large individual variations (Fig 4). $C(a-v)_{O_2}$ and O_2ER had no clinically important changes.

Correlation between Variables

LVSWI correlated positively with VO_2 in the SPHA and NS groups but not in the FFP group. $\overline{PCWP}$ and $COP-\overline{PCWP}$ difference did not correlate with VO_2, $\dot{Q}_A/\dot{Q}_T$ or Pa_{O_2}.

Biochemical Data of FFP and SPHA

Albumin was 4.71 ± 0.155 gr/dl in SPHA and 4.06 ± 0.089 in FFP. COP was 20.02 ± 1.34 torr in SPHA and 30.56 ± 0.984 in FFP. Total proteins were 4.86 ± 0.166 gr/dl in SPHA and 5.65 ± 0.147 in FFP. Citrate levels were 11.07 ± 0.85 mg/dl in SPHA and 210 ± 10 in FFP.

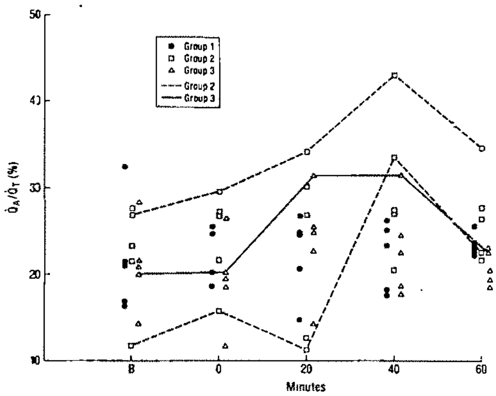

FIG 4. $\dot{Q}_A/\dot{Q}_T$ values of all patients before and after infusion of the three volume expanders. Solid and dotted lines indicate changes observed in three patients who developed significant hypoxemia (Pa_{O_2}: 46 to 54 torr) after volume expansion.

Discussion

Of all the variables that could be affected by administration of intravenous fluids, hemodynamic pressures were the least affected. Rapid administration of fluids increased only $\overline{RA}$ and $\overline{PAP}$ by 3 to 4 torr. These changes were statistically significant but clinically irrelevant, and return to baseline values was completed within 20 minutes. Blood chemistries indicated a significant fall in ionized calcium (Ca^{++}) which was inversely correlated with the increase of serum citrate. The fall of Ca^{++} was predictably most pronounced in the patients receiving FFP (Fig 2) since the citrate content of FFP is equal to that of bank blood.[12] However, as previously demonstrated, no adverse hemodynamic effects followed the changes of Ca^{++}.[13]

Of particular interest were changes in colloid osmotic pressure (COP). COP and the difference COP-$\overline{PCWP}$ increased in patients receiving SPHA (Fig 1) or FFP (Fig 2) and decreased in those receiving NS (Fig 3), as was anticipated. However, no correlation could be found between COP and COP-$\overline{PCWP}$ difference and changes in Pa_{O_2} or $\dot{Q}_A/\dot{Q}_T$. We were thus unable to confirm in our patients a clinically significant increase in $\dot{Q}_A/\dot{Q}_T$ once the Starling equation had been modified by reducing the difference between colloid osmotic pressure and hydrostatic pressure ($\overline{PCWP}$).[14] Furthermore, if elevation of COP is considered important, FFP infusion was associated, in our patients, with a greater and more lasting increase of COP. Considering the high cost of SPHA and our inability to demonstrate advantageous effects as compared to FFP, we believe its indications to be more restricted than some authorities currently recommend.[14]

The most significant changes effected by intravascular volume expansion were those involving hemodynamic flow and oxygen transport and uptake. FFP infusion produced in all patients a sustained, marked increase in CI, SI, and LVSWI as well as $\dot{V}O_2$ and $\dot{C}O_2$ (Fig 2). SPHA had scarcely any effect on these variables (Fig 1), whereas NS did not affect flows and significantly decreased $\dot{V}O_2$ and $\dot{C}O_2$ (Fig 3). Different hemodynamic effects might have been obtained if larger volumes of NS had been infused. However, to compensate for the distribution throughout the extravascular volume, approximately 2000 ml of NS would have to be administered to afford the same increase of intravascular volume as would result from 500 ml of FFP. We felt that such a large infusion was impractical to administer over 20 minutes and perhaps unsafe. Both FFP and NS caused an increase of $\dot{Q}_A/\dot{Q}_T$ in all patients studied (Figs 2 and 3). Although in general not clinically relevant, this increase was significant in three patients (Fig 4). However, $\dot{Q}_A/\dot{Q}_T$ returned to baseline values in all patients within 60 minutes, whereas the hemodynamic effects of FFP lasted much longer.

We conclude that FFP should be administered when rapid volume expansion is needed, pre- or intraoperatively, if the aim is to increase cardiac output and oxygen availability. In patients with interstitial lung disease however, precautions should be taken to minimize the increased $\dot{Q}_A/\dot{Q}_T$ for 40 to 60 minutes. Raising the concentration of inspired oxygen and/or adding 3 to 5 cm H_2O of PEEP may be advisable. From our observations, we do not think that the other volume expanders investigated had consistently advantageous effects.

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Epidural Analgesia and Nitrogen Balance

Postoperative nitrogen balance was monitored in 12 patients undergoing elective abdominal hysterectomy under either epidural analgesia (bupivacaine) or general anesthesia (halothane). Epidural analgesia was maintained throughout the first 24 hours following surgery. The mean cumulative 5-day nitrogen losses were significantly lower after epidural analgesia than after general anesthesia. Nitrogen sparing presumably results from inhibiting the stress-induced release of catabolic hormones, since epidural analgesia abolished postoperative hyperglycemia and increase in plasma cortisol concentrations. No adverse effects of inhibiting the stress response were observed. Neurogenic stimuli thus play a crucial part in the catabolic response to surgery. Inhibiting the endocrine-metabolic response to trauma by neurogenic blockade may reduce the morbidity precipitated in high-risk patients by the catabolic response to surgery. *(Brandt MR, Fernandes A, Mordhorst R, et al: Epidural analgesia improves postoperative nitrogen balance. Br Med J 1:1106-1108, 1978)*

Propranolol Therapy and Surgery

The relationship between long-term propranolol therapy and subsequent coronary bypass operation was prospectively investigated in 119 patients in three groups: propranolol therapy continued in full dosage to operation (38 patients; group A), propranolol therapy discontinued or tapered 24 to 72 hours preoperatively (40 patients; group B), and no preoperative propranolol therapy (41 patients; control group). During preoperative hospitalization, one patient in each of group A and the control group suffered an increase in anginal symptoms compared with 15 patients in group B, three of whom also had new ventricular arrhythmias. During anesthesia, up to the period of cardiopulmonary bypass, 26% of patients in group A showed signs of ischemia (e.g., ST segment deviation or ventricular arrhythmias) as compared with 51% of the control group and 70% of group B. Hypotension and bradycardia were not more common in group A patients. No differences among groups were noted in ease of emergence from bypass, need for cardiac stimulants, or mortality. These data indicate, for the population and circumstances studied, an advantage for the continuation of preoperative propranolol therapy. *(Slogoff S, Keats AS, Ott E: Preoperative propranolol therapy and aortocoronary bypass operation. JAMA 240:1487-1490, 1978)*

ANESTH ANALG
58:19-22, 1979

Nonlinear Antagonism of Anesthesia in Mice by Pressure

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SMITH, R. A.,SMITH, M., EGER, E. I., II, HALSEY, M. J., AND WINTER, P. M.: Non-linear antagonism of anesthesia in mice by pressure. Anesth Analg 58: 19-22, 1979.

Previous studies have shown a rectilinear antagonism by pressure of nitrous oxide or isoflurane anesthesia in mice (pressure reversal). Since a rectilinear pressure reversal is predicted by the critical volume hypothesis for anesthesia, we examined this phenomenon with two other gases. We measured the doses of argon or nitrogen which abolished the righting reflex in 50% of animals (ED_{50}) at various high pressures produced by the addition of helium. The ED_{50} values of argon and nitrogen alone are 16.7 ± 1.37 and 38.3 ± 1.62 atmospheres absolute (ATA). Fifty-five percent more argon and 27% more nitrogen is needed to produce anesthesia at 100 ATA. However the increasing anesthetic requirements with pressure were curvilinearly related to pressure, rising most steeply at pressures near the ED_{50} without helium. This suggests that the pressure reversal of anesthesia is not simply a reciprocal anesthetic expansion-pressure compression phenomenon as predicted by the critical volume hypothesis. It suggests that anesthetics and pressure act at different sites.

Key Words: THEORIES OF ANESTHESIA: pressure reversal; HYPERBARIA: pressure reversal.

CRITICAL volume hypothesis for anesthesia suggests that dissolved anesthetic molecules cause anesthesia by producing a 0.5% volume expansion of some site in a cellular membrane crucial to neuronal activity.[1,2] Since all matter is compressible, very high pressures (tens to hundreds of atmospheres) can restore the expanded membrane to its original dimensions and thereby cause awakening. Johnson et al[3,4] showed that several drugs diminish the luminescent intensity of *Photobacterium phosphoreum* and the luminescence is restored by application of high hydrostatic pressure. Similarly, ethanol-anesthetized tadpoles regained their normal swimming activity upon application of high hydrostatic pressure.[5,6] Both of these observations can be explained by the critical volume hypothesis. Furthermore, in model solvents the volume expansions induced by anesthetic doses at ED_{50} can be reversed by pressure, and the pressure required is similar for various agents.[2] The predictive power of the critical volume model has given the hypothesis considerable support and has established the use of high pressure as a tool with which to probe the mechanism of anesthesia. However, in this paper we report evidence that suggests that the relationship between pressure and anesthesia may not be as simple as originally thought.

Methods

We studied the effect of high helium pressures on

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anesthesia achieved in mice with argon or nitrogen. The experiments were conducted in a 20-L cylindrical stainless steel pressure chamber fitted with a large viewing window. The oxygen partial pressure was kept between 0.6 and 1.2 ATA and carbon dioxide was removed continuously by circulating chamber gases through soda lime. Gas samples were withdrawn from the chamber and analyzed by gas chromatography to check the partial pressures of the gases added. The chamber was equipped with eight cylindrical wire mesh cages in which individual unrestrained mice could be rotated in either direction at 4 rpm. Chamber temperature was monitored and adjusted to maintain rectal temperatures between 37 and 38 C in three additional restrained mice. Our criterion of anesthesia was the loss of righting reflex which correlates well with other indices of anesthetic potency.[7] After equilibration for 30 minutes at any given dose, animals that fell over and rotated through 360 degrees during two revolutions in a five-revolution sequence were considered anesthetized and scored zero. The quantal dose response data were analyzed using a logit transformation[8] to give partial pressures (with standard errors) which abolished the righting reflex in 50% of the animals tested, i.e. the median effective dose (ED_{50}). Dose response curves and ED_{50} values were then redetermined in the presence of increasing partial pressures of helium.

Results

The addition of helium to argon or nitrogen antagonized the anesthetic effect of these gases but in a curvilinear fashion (Table; Fig 1). The control ED_{50} of argon alone was 16.7 ± 1.37 ATA and nitrogen was 38.3 ± 1.62 ATA. The data were normalized to percentage of increase in ED_{50} by dividing each of the ED_{50} values at pressure by the respective control ED_{50} obtained when no helium was present (table). These normalized values are plotted against pressure in Figure 1.

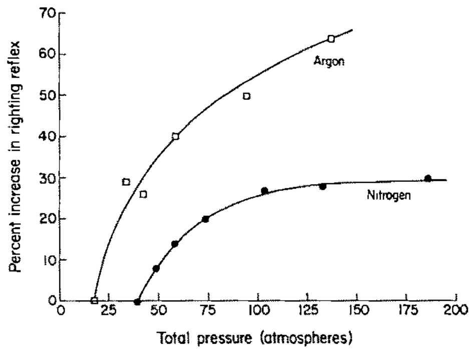

FIG 1. Percentage of increase in ED_{50} for loss of righting reflex in mice caused by argon (□) and nitrogen (●) as a function of total pressure.

TABLE
ED_{50} Values for Loss of Righting Reflex in Mice for Argon and Nitrogen at Different Total Pressures.

Agent	Total pressure ATA	ED_{50} ± SE ATA	No. of mice	% ED_{50} increase over control	f_a/f_{50} (see text)	% expansion of olive oil
Argon	17.7	16.7 ± 1.37	77	0	1.00	0.417
	33.6	21.6 ± 1.73	23	29	1.30	0.552
	42.5	21.1 ± 3.62	22	26	1.26	0.554
	58.4	23.4 ± 2.64	23	40	1.39	0.624
	94.5	25.1 ± 3.22	32	50	1.48	0.698
	136.9	27.4 ± 8.79	16	64	1.58	0.780
Nitrogen	39.3	38.3 ± 1.62	80	0	1.00	0.519
	48.7	41.3 ± 3.49	24	8	1.08	0.565
	58.1	43.8 ± 3.92	24	14	1.14	0.603
	73.6	46.1 ± 2.22	32	20	1.20	0.644
	103.5	48.7 ± 4.94	24	27	1.25	0.698
	133.0	49.2 ± 5.33	24	28	1.24	0.724
	186.4	49.7 ± 3.81	13	30	1.19	0.762

The extent of pressure reversal differed between the two agents. At 100 ATA total pressure, for example, argon ED_{50} was elevated by 55% and the nitrogen ED_{50} by 28%.

Finally, the potencies of argon and nitrogen were not linearly related to the total pressure in the pressure range below 100 ATA where linear relationships were previously found for nitrous oxide and isoflurane in mice[9,10] and recently found for argon and nitrogen in mice[11] and for several agents in newts.[2]

Discussion

Our argon and nitrogen ED_{50} values are about 10% higher than those reported by Miller et al.[7] This may have resulted from the failure, in these earlier studies, to account for the reduction in core temperature experienced by mice at high pressures when the environmental temperature is less than 35 to 36°C. Our ED_{50} values are in good agreement with the most recent values obtained by Miller et al.[11]

The ED_{50} values for argon and nitrogen predicted from oil solubilities are 15 ATA and 31 ATA, respectively. Our higher ED_{50} values can be explained if the high pressure required to achieve anesthesia with these gases exerts a slight pressure antagonism of their anesthetic effect and thereby reduces their potencies.

The difference in degree of pressure reversal at 100 ATA for these two agents is dissimilar from that found with nitrous oxide (46%)[9] and isoflurane

(61%).[10] This suggests that the pressure-anesthesia interaction may be related to properties specific to individual agents.

The critical volume hypothesis for anesthesia predicts a linear relationship between the dose of an anesthetic normalized to its ED_{50} (i.e., the dose Pa/P_{50}) and the applied pressure of helium above the pressure of the anesthetic present (P_T-Pa).[2] Two corrections must be applied to the data to allow for the behavior of real gas as it deviates from ideal gas laws and also to allow for the dependence on pressure of solubility.[2] The first correction demands that anesthetic partial pressures should be changed to calculated fugacities which may be thought of as idealized partial pressures. Thus our results are plotted in Figure 2 as the idealized dose ratio fa/f_{50} versus the applied pressure of helium P_T-Pa. These lines are clearly nonlinear. Miller et al[11] reported that argon and nitrogen were antagonized linearly by pressure although their data are less extensive than ours. Those authors accept the validity of our nitrogen results and that they deviate significantly from linearity (K. W. Miller, personal communication). However, the important point is that when the corrections are made, the deviations are exacerbated rather than ameliorated and this suggests that other factors must be considered in the pressure-anesthesia interaction. This is further demonstrated if the expansion by anesthetic of a model solvent such as olive oil at each anesthetic ED_{50} is plotted against pressure (Fig 3). These are easily calculated from the physical properties of the olive oil and of the dissolving gases as shown by Miller et al.[2,11] Linear regression gives a slope of 2×10^{-5} ATA^{-1} which compares well to the compressibility of olive oil (6×10^{-5} ATA^{-1}) and an intercept of 4.7×10^{-3} (i.e., 0.47%) which represents the fractional expansion of olive oil at anesthesia at 1 ATA. The correlation coefficient is 0.917. If a quadratic regression is performed, a much improved fit is achieved with a correlation coefficient of 0.981. If the variance apportioned to the parameters of regression then is compared to the residual variance by an F-test, both parameters of the quadratic regression have high significance ($p < 0.001$). However, the physical significance of the parameters in terms of the critical volume hypothesis is lost when the fit is improved in this manner, and this carries the important implication that the critical volume hypothesis does not adequately describe the pressure-anesthesia interaction.

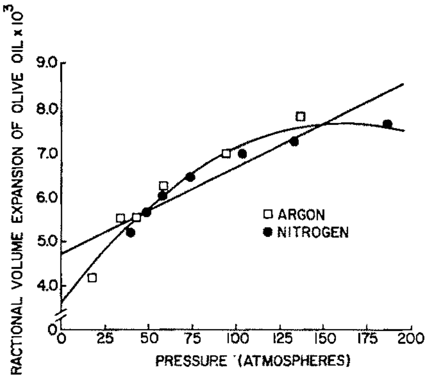

FIG 3. Fractional volume expansion of olive oil at an ED_{50} of argon (□) and nitrogen (●) versus total pressure. The straight line is a linear regression of the points and the curved line is a quadratic regression.

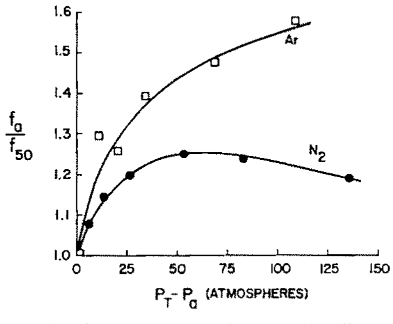

FIG 2. Dose ratio after correction for non-ideality of gases and dependence of solubility on pressure (f_a/f_{50}) versus applied pressure of helium (P_T-P_a) for argon (□) and nitrogen (●).

This simple view of anesthesia-expansion, pressure-compression is one in which expansion and compression occur uniformly over the hydrophobic site of action. This is unlikely to be true. There is much evidence that the lipids in membranes are in equilibrium between a liquid-like and a solid-like phase.[12-14] Moreover the lipid composition is probably heterogeneous over the membrane.[15] Although compressibilities of organic hydrocarbon liquids or fatty acids are constant over the range of pressures we use, compressibilities at melting points are indeterminate since pressure itself affects the melting point. Therefore we cannot impute similar properties to membrane lipids close to their melting points, and it would not be surprising if compressibility were to vary both within the membrane and with pressure. It appears too simplistic to suggest that the effect of expansion produced by nitrous oxide or isoflurane is nicely balanced by the compression that pressure exerts on all sites whereas with nitrogen or argon, expansion and compression are not exactly balanced at all sites. However, the curvilinearity of the pressure reversal must be taken as evidence against the idea of a singular mechanistic reciprocity between anesthesia and pressure.

Since many anesthetics are known to produce excitatory effects, presumably by depressing inhibitory neurons, it is very probable that anesthetics have at least two sites of action, if not more, in the brain. Similarly, pressure must affect all sites whose activity involves a volume change. Several studies suggest a multiplicity of pressure effects at sites different from those affected by anesthetics. Miller[16] analyzed quantitative data for the pressure dependence of anesthesia as measured by the rolling response in mice and the anesthetic dose dependence of convulsion threshold pressure in mice exposed to different gases. Using the physical characteristics of membrane model solvents, he concluded that the compressibility of the site (or sites) mediating convulsions was 2 to 5 times that (or those) mediating anesthesia, indicating that these two sites (or groups of sites) have different properties and are separate physiologically if not separate anatomically. In a recent study of the high pressure nervous system syndrome and anesthesia in mice, two distinct sites mediating spasms and anesthesia have been identified by analysis of the end points studied in terms of the critical volume hypothesis.[17] Halsey et al[18] showed that hydrostatic pressure reverses the depressant effects of a wide range of drugs including anesthetics, narcotics and tranquilizers in tadpoles. Since all of these compounds are unlikely to have the same primary site of action, this suggests that the effect of pressure may be to increase all central nervous system excitability. Further evidence is found in the fact that the slope of the phenobarbital dose response curve for the loss of righting reflex in mice is significantly steeper at 100 ATA helium pressure than at 1 ATA,[19] suggesting something more complicated than simple reciprocal or competitive antagonism. Although pressure reversal of anesthetic-induced conduction failure has been shown in axonal preparations,[20] pressure potentiates anesthetic effects in synaptic transmission.[21] All of these studies suggest that the interaction is not truly reciprocal and that the primary sites of action of pressure and anesthesia are independent.

In summary, we have shown nonlinear pressure reversal of argon or nitrogen anesthesia in mice. This result is different from earlier studies with other agents and contrary to what other authors have found with these same agents using fewer animals. Our results suggest that the pressure reversal of anesthesia is not a simple phenomenon associated with expansion and compression of membranes, as predicted by the critical volume hypothesis, and suggest that anesthetics and pressure may act at different sites.

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Echocardiographic Analysis of Human Left Ventricular Diastolic Volume and Cardiac Performance during Halothane Anesthesia

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Using M-mode echocardiography we found that 0.5, 1.0, and 1.5% end-tidal halothane induced dose-related increases in left ventricular volume and decreases in left ventricular performance in seven normal unpremedicated subjects. During controlled respiration with normocarbia, the diastolic minor axis of the heart, which is related to the cube root of left ventricular volume, increased to a maximum of 107.7 ± 1.9 (% ± SE of control) at 1.5% end-tidal halothane from a control value of 43.5 ± 1.3 (mm ± SE). Two ejection-phase performance variables, percentage shortening and mean velocity of circumferential shortening decreased to 60.1 ± 6.1 (% ± SE of control) and 62.4 ± 6.5, (% ± SE of control) at 1.5% halothane from respective control values of 29.7 ± 2.61 (% ± SE and 0.94 ± 0.08 (circumferences/second ± SE). Surgical stimulation did not significantly affect these changes. Under these experimental conditions, we conclude that halothane dilates the heart, and that echocardiography can be used to monitor the depressant effect of halothane on the heart.

Key Words: MEASUREMENT TECHNIQUES: echocardiography; HEART: echocardiography, myocardial function; ANESTHETICS, Volatile: halothane.

M-MODE echocardiography consists of the use of painless, noninvasive ultrahigh frequency sound waves to examine the heart. In the M or "time-motion" mode, both the distance between cardiac structures and their movement with time are displayed. Ultrasound waves of 2 to 2.5 Mhz frequency are beamed in pulses of approximately 1 microsecond duration from a piezoelectric, half-inch diameter, transducer hand-held on the external chest wall in the second to fifth intercostal space within 3 or 4 cm of the left sternal border. Echoes from cardiac structures are received by the same transducer and processed electronically to appear as dots on a storage oscilloscope. The dots are transformed into wavy lines by the sweep of the oscilloscope. Because both the sweep time of the oscilloscope and the velocity of sound in human tissues are known, the wavy lines are calibrated for both time and distance. The physical characteristics of ultrasound affect its use in practice; it is scattered by the numerous gas-tissue interfaces in the

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lungs and attenuated by bone. Its high frequency, however, permits resolution of echoes from interfaces approximately 1 mm apart.[1]

As noted by Wexler and Pohost,[2] echocardiography has potentially important applications in anesthesiology in evaluation of acute physiologic perturbations induced by general anesthetics. We employed echocardiography to investigate the following two questions. First, can echocardiography replace invasive measurements of cardiovascular function? As a first step toward an answer, we measured echocardiographic performance variables under anesthesia, and compared our results to previously published invasively obtained data. Second, we examined whether left ventricular end-diastolic volume (LVEDV) changed during halothane anesthesia in man.

Methods and Materials

Seven fasting, unpremedicated, A.S.A. I male patients, ages 23 to 32 years, were studied in the supine position. The project was approved by the University of California San Francisco Committee on Human Research. Each patient gave informed consent. All subjects had negative cardiac histories and physical examinations, normal electrocardiograms and chest radiographs, and were scheduled for elective surgery below the umbilicus. Patients were interviewed the evening prior to surgery, taught awake controlled ventilation, and underwent echocardiography. Patients with insufficiently clear echocardiograms were eliminated from the study.

On the morning of surgery, a slow intravenous infusion (<200 ml total during the study) of 5% dextrose in lactated Ringer's solution was begun. We applied a blood pressure cuff, standard limb electrocardiogram leads, and an echocardiographic transducer, the position of which, marked in indelible ink, was kept constant in the fourth or fifth intercostal space near the left sternal border. Echocardiographic, pulse rate, and blood pressure measurements were performed during awake spontaneous ventilation with 100% oxygen and again during awake controlled ventilation by mask with 100% oxygen through the standard anesthesia circle system used throughout the study. Awake controlled ventilation was chosen as the control state. Halothane-oxygen anesthesia was induced during spontaneous ventilation. Following induction, controlled ventilation by mask was reinstituted to keep end-tidal P_{CO_2} identical with the control end-tidal CO_2 value (Beckman LB-2). Because of concern that the end-tidal CO_2 under anesthesia might not reflect the arterial P_{CO_2} as well as an awake end-tidal CO_2 does, peripheral venous P_{CO_2}'s were drawn from the intravenous line, without a tourniquet, after discarding as dead space the first 10 ml of blood. These peripheral venous P_{CO_2}'s were within 5 torr of the simultaneous end-tidal value. France et al[3] have shown a mean ± SD difference during general anesthesia of only 0.9 ± 2.3 torr between arterial and forearm or hand venous P_{CO_2}.[3] Stable end-tidal halothane concentrations (Beckman LB-1) were maintained for at least 10 minutes before measurements were made at concentrations of 0.5%, 1.0%, and 1.5% preoperatively and 1.0% and 1.5% intraoperatively. Control and anesthetic echo measurements were all made at end-expiration.

Deviations from the experimental protocol were the following. Echocardiograms for two of the seven patients could not be obtained during awake controlled ventilation presumably due to increased functional residual capacity and scattering of ultrasound. Awake spontaneous ventilation was chosen as their control period, since (see results below) data with spontaneous and with controlled respiration were not found to be significantly different in the awake state. Movement during 0.5% halothane preoperatively prevented testing in three of the seven patients. One patient's results at 1.0% halothane intraoperatively were discarded due to junctional rhythm.

We used a Unirad model C series 100 Diagnostic Echoscope System equipped with a 2.25 Mhz, 7.5-cm focal length transducer, and a Tektronix model 4601 strip-chart recorder. Recordings were made at a paper speed of 50 mm/sec. Fig 1 shows the transducer's position relative to the heart. The central beam of ultrasound through the left ventricular internal dimension (LVID) has been drawn in. LVID is defined in this study as the distance between septum and posterior wall at a level through the left ventricle where echoes either from both mitral valve leaflets or from their chordae tendineae may be recorded.[4]

Variables at each level of halothane measured were pulse rate, systolic and diastolic arterial pressure, LVID at end-diastole and end-systole ($LVID_d$ and $LVID_s$), and left ventricular ejection times.[5] Each echocardiographic variable was analyzed using 3 to 5 sinus beats. The peak of the electrocardiographic "R" wave indicated end-diastole. End-systole was defined by the most anterior movement of the left ventricular posterior wall.[6] Two ejection-phase performance variables, percentage shortening of LVID with systole (% shortening) and mean velocity of circumferential shortening (mean Vcf) were calculated. Mean Vcf is the fractional shortening of LVID with systole divided by the left ventricular ejection time. Mean Vcf may be thought of as the normalized mean velocity of shortening of an imaginary circumferential strip of cardiac muscle of diameter LVID. Mean Vcf = $(LVID_d - LVID_s) \div (LVID_d \times (\text{ejection time}))$; % shortening = $100 \times (LVID_d - LVID_s) \div LVID_d$. Decreases in % shortening and mean Vcf imply worsening ventricular function.

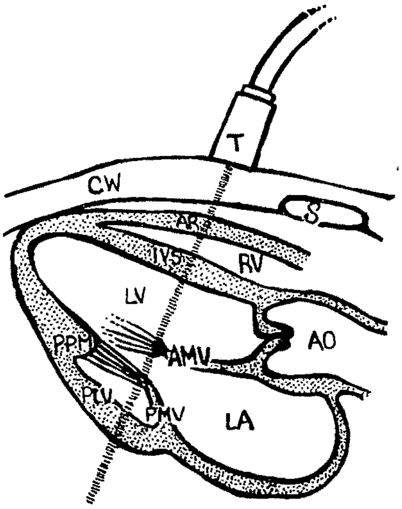

Fig 1. Structures identified by the echocardiograph An ultrasonic beam has been drawn along LVID (see text). T, transducer; CW, chest wall; S, sternum; AR, anterior wall of right ventricle; RV, right ventricular cavity; IVS, interventricular septum; LV, left ventricular cavity; AO, aortic root; AMV, anterior mitral valve apparatus; PMV, posterior mitral valve apparatus; PPM, posterior papillary muscle; PLV, posterior left ventricular wall; LA, left atrium.

TABLE 1

Preanesthetic Control Values of Measured Hemodynamic and Echocardiographic Variables (mean ± SE)

No. of subjects	7
Pulse (beats/min)	67 ± 2
Mean arterial pressure (torr)*	86 ± 3
$LVID_d$ (mm)	43.5 ± 1.3
% shortening (%)	29.7 ± 2.6
Mean Vcf (circumferences/second)	0.94 ± 0.08

* Mean arterial pressure = diastolic pressure + ⅓ (systolic pressure − diastolic pressure).

Ventricular volumes and cardiac outputs were calculated using the prolate ellipsoid model of the left ventricle in which LVID is assumed to be the minor axis of the ellipsoid and volume is taken to be LVID cubed. Fombo et al[7] provide a geometric rationale for this model.

Results

Control data for hemodynamic and echocardiographic variables are presented in Table 1. The values are within published normal limits: $LVID_d$ 33 to 58 mm,[8] % shortening 28 to 41%,[8] and mean Vcf with echo ejection time 0.92 ± 0.15 (SD) circumferences/second.[4] No statistically significant difference ($p > 0.1$ by paired t-test) was seen in these hemodynamic and echocardiographic variables between awake spontaneous and awake controlled ventilation, although four of the five subjects showed a small mean decrease in $LVID_d$ (<2 mm) during awake controlled ventilation.

During anesthesia, before surgery, we found evidence of cardiac depression via the echocardiograph (Table 2). Fig 2 is a composite echocardiograph from one patient illustrating this depression. $LVID_d$ increased under deep anesthesia, and a dramatic decrease in the amplitude of contraction of septum and posterior wall occurred. As indicated in Table 2, we found no change in pulse rate, but statistically significant increases in $LVID_d$, and decreases in blood pressure, percentage shortening, and mean Vcf in this

TABLE 2

Mean Pulse, Blood Pressure, and Echocardiographic Variables during Anesthesia and Surgery (Expressed as % of Control ± SE)

	Preoperative			p value*	Intraoperative	
	0.5% halothane	1.0% halothane	1.5% halothane		1.0% halothane	1.5% halothane
No. of subjects	4	7	7		6	7
Pulse	98.3 ± 3.9	93.1 ± 3.1	93.4 ± 6.4	>0.5	111.2 ± 6.3	111.7 ± 6.5
Mean arterial pressure	88.7 ± 5.9	82.5 ± 3.6	76.0 ± 5.8	<0.005	99.2 ± 7.7	84.8 ± 7.9
$LVID_d$	104.3 ± 1.7	106.0 ± 1.8	107.7 ± 1.9	<0.01	107.3 ± 1.9	104.7 ± 1.9
% shortening	82.0 ± 11.0	74.9 ± 5.2	60.1 ± 6.1	<0.0005	71.9 ± 5.9	65.8 ± 4.5
Mean Vcf	85.0 ± 14.5	76.6 ± 6.3	69.7 ± 6.2	<0.005	84.8 ± 10.1	78.5 ± 6.3

* p value of an analysis of variance on preoperative and control data. Statistical significance considered to be $p < 0.05$. Student-Newman-Keuls analysis fails to detect any significant difference between concentrations of halothane for any variable. Dunnett's test shows significant difference between each variable and the awake control state at every halothane concentration.

preoperative period. These changes in echocardiographic variables appeared to be dose related (Figs 3 to 5) but Student-Newman-Keuls analysis failed to detect any difference between these variables at different halothane dose levels, although each variable at each level was statistically different from the control state (Dunnet's test $p < 0.05$). Fig 6 shows a statistically significant correlation between the two performance variables, mean Vcf and % shortening, before, but not during surgery.

Table 2 and Figs 3 to 5 also show increases observed during surgery in pulse and blood pressure, but minimal effect on LVID_d, % shortening, and mean Vcf. We did not perform statistical analysis on the intraoperative data since the surgical stimulation was not standardized.

Discussion

Does echocardiography accurately measure ventricular volumes and cardiac outputs derived from those volumes in this experimental setting? We believe that it does not accurately measure the absolute values of these volume-derived variables and that to represent that it does may be misleading. To emphasize this contention, we have chosen to extrapolate our echocardiographic data to cardiac output and volume data, using published methods,[7] which happen to yield unusually low values. If we had used other regression equations we could have obtained more conventionally accepted values for cardiac output. The reason for this wide range of regression equations is inherent in the method of echocardiography. Echocardiography does not measure left ventricular volume directly since the echo beam "sees" in only one dimension, and volume is calculated using either the prolate ellipsoid model, or using published regression equations obtained with simultaneous invasive measurements. Linhart et al[9] summarize the difficulties in extrapolating LVID (one dimension) to volume (three dimensions). The mean control LVEDV of our subjects could be anywhere from 82 to 148 ml depending on which regression equation is used[10] despite the fact that our mean control LVID_d was in the midrange of normal!

The confusion in extrapolating echocardiographic

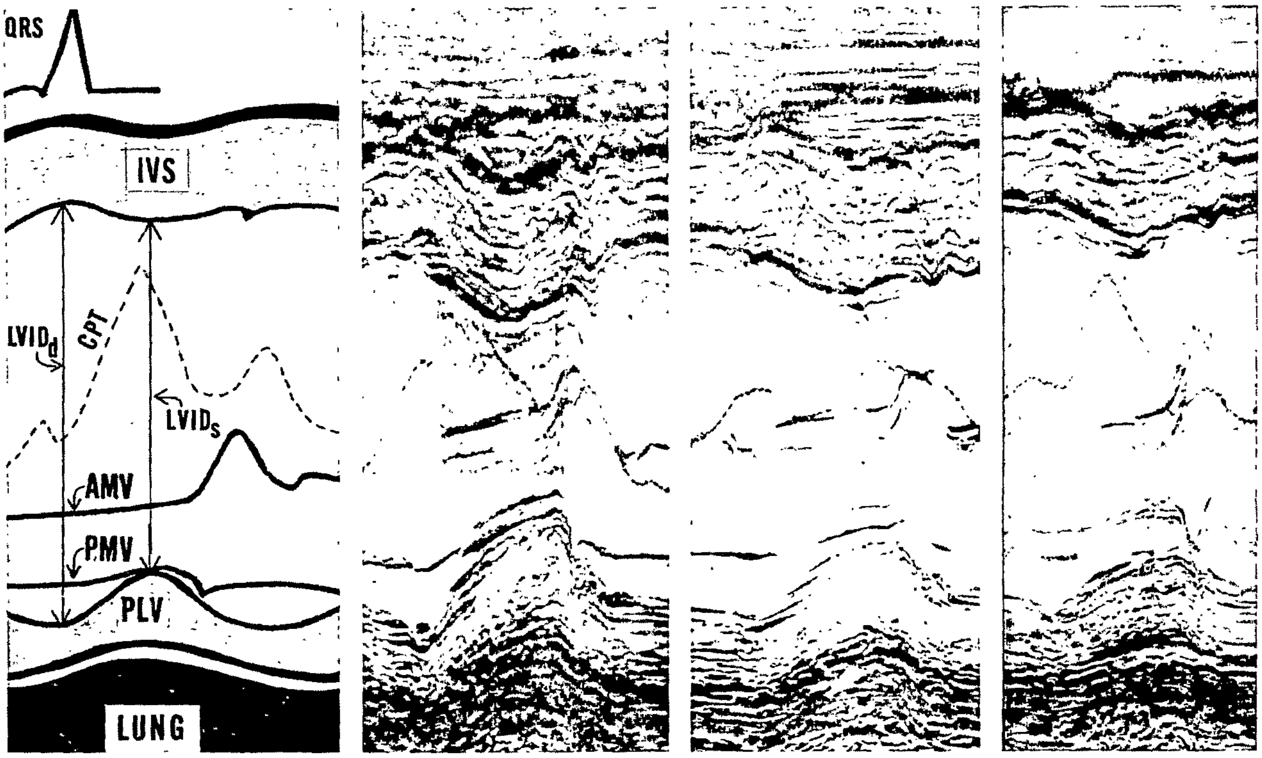

FIG 2. Preoperative changes in one patient's echocardiogram with halothane. The left panel is a labeled schematic drawing of an echocardiogram with these abbreviations: QRS, electrical systole from an electrocardiogram; IVS, interventricular septum; CPT, carotid pulse tracing; AMV, anterior mitral valve apparatus; PVM, posterior mitral valve apparatus; PLV, posterior left ventricular wall. LVID_d and LVID_s represent distances (see text). The other panels are photographs at constant magnification of the patient's echocardiogram awake, during 0.5% halothane and during 1.5% halothane, respectively, in the absence of surgery.

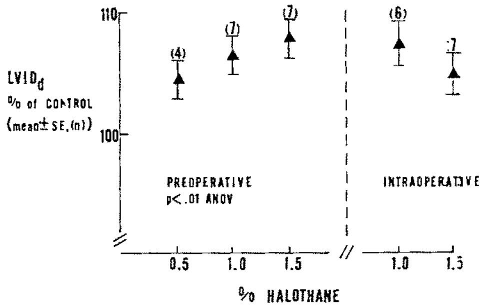

FIG 3. Preoperative and intraoperative changes in LVIDd with increasing halothane dose.

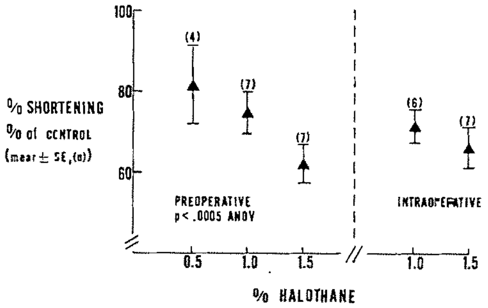

FIG 4. Preoperative and intraoperative changes in percentage shortening with increasing halothane dose.

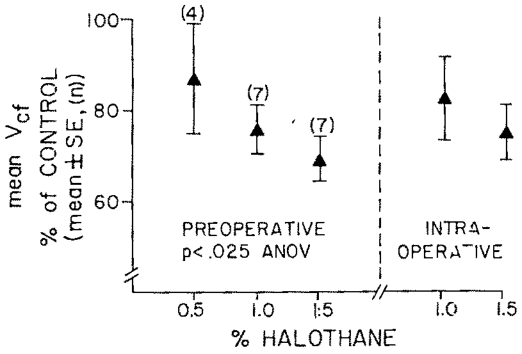

FIG 5. Preoperative and intraoperative changes in mean Vcf with increasing halothane dose.

data to cardiac volume is further extended by the lack of a precise standard for comparison with data derived from invasive techniques. Yang et al[10] have summarized the wide range of reported normal invasively obtained LVEDV. Expressed as milliliters per square meter of body surface area, cineradiographic methods yield a range of LVEDV from 50 to 90[11] and dilution methods yield a range from 70 to 210.[12, 13] Thus, criticism of echocardiographic ventricular volumes must admit that invasive methods also give widely differing results.

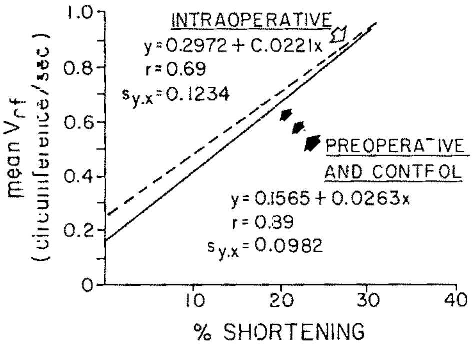

FIG 6. Correlation of the two performance variables, percentage shortening and mean Vcf, at every point of data collection with % shortening plotted on the *x* axis and mean Vcf on the *y* axis. *r* = Correlation coefficient; Sy.x = standard error of the estimate.

We believe that the depression of cardiac performance and increase in LVEDV found in this study should be less controversial, and that echocardiography accurately reflects acute changes in these variables. For the cardiac output to increase and the LVEDV to fall during halothane anesthesia while percentage shortening and mean Vcf are observed to decrease and $LVID_d$ is observed to increase, would require selective cardiac dilation in one dimension and shrinkage in another, a unique and unlikely pharmacologic event.

Cardiac Depression

In order to compare the magnitude of cardiac depression observed in this study with invasively obtained data, we calculated cardiac outputs. We compared echocardiographic outputs to those found in a similar group of human subjects by Eger et al,[14] who used dye dilution. Echocardiographic outputs were calculated by multiplying heart rate by stroke volume. Cardiac output equals heart rate times $[(LVID_d)^3 - (LVID_s)^3]$. We found a mean control cardiac index of 2.02 ± 0.24 (SE) L/min-m^2, below that of Eger's mean 3.17. Beside the problems of extrapolating echocardiographic data to volume data mentioned above, some of the differences in control outputs between the two techniques may have resulted from less apprehension in our noninvasively studied subjects. Although Eger's subjects also had a mean age in the 20s, control values for pulse and mean arterial pressure expressed as mean ± SE were 77 ± 3 beats/minute and 95 ± 2 torr, respectively, in Eger's study[14] compared with our patients' 67 ± 2 beats/minute and 86 ± 3 torr. However, at the two anesthetic concentrations common to the two studies, 1.0% and 1.5%, Eger's data for patients anesthetized less than 1 hour, as ours were, yield a calculated cardiac output slope (change in cardiac output/change in halothane concentration) of −19 compared to ours of −20. This indicates that echocardiography demonstrates the same magnitude of anesthetic depression of the heart as does an invasive technique.

The finding of parallel changes in mean Vcf and percentage shortening before surgery in this study suggests that only one of these performance variables may be needed to demonstrate cardiac depression during halothane anesthesia. But the poorer correlation of these performance variables during surgery argues against that possibility. More data are needed.

Cardiac Volume

Our echo data in man were compared to two dog studies using invasive methods, since no published invasive data on human LVEDV under anesthesia could be found. In Table 3, the data from all three studies were normalized to make the control state 100%. At the lowest halothane concentration, only the echo data show an increase in volume, whereas at 1.0% and 1.5% our echo data lie between the other two studies, if Hamilton's data are interpolated to a value at 1.5%.

The observed ventricular dilation under halothane anesthesia has relevance to the consideration of myocardial oxygen consumption. Sonnenblick et al[17] found that intramyocardial tension, heart rate, and contractile state were major determinants of myocardial oxygen consumption. The use of aortic or arterial pressure alone to estimate intramyocardial tension ignores the fact that tension is also proportional to radius in the LaPlace relation. Thus, reduction in arterial pressure seen with halothane anesthesia does not produce a proportionate reduction in oxygen consumption since the pressure decrease is accompanied by dilation. The overall change, however, favors a decrease in oxygen consumption. The maximum radius change we measured in this study, about 8%, accompanied a mean arterial pressure decrease of about 24%.

TABLE 3
Comparisons of Published Reports on Mean Left Ventricular Diastolic Volumes during Halothane Anesthesia as % of Control

Study:	Hamilton et al[15]	Rusy et al[16]	Present study
Subjects:	Dogs	Dogs	Humans
Methods:	Thermal dilution	Cineradiography	M-mode echo
		%	
End-tidal halothane			
0.5–0.6%	90	—	113
1.0–1.2%	122	101	120
1.5%	—	109	126
1.8%	160	—	—
2.0%	—	116	—

Since this paper was submitted for publication, two papers employing echocardiography under halothane anesthesia have appeared. Barash et al,[18] who studied children, found similar cardiac depression, with mean Vcf falling to 85%, 78%, and 72% of control value at 0.5%, 1.0%, and 1.5% inspired halothane, respectively. This study did not measure end-tidal or arterial concentrations, so that the exact dose of halothane received by their patients is unknown. Their patients also breathed nitrous oxide, were premedicated, and had unknown P_{CO_2}'s. Barash et al report no statistically significant change in LVEDV, although their Fig 5 shows about a mean 3% increase at 1.5% halothane. A second paper, by Rathod et al,[19] reported that in adults mean Vcf and percentage shortening were diminished to 66% and 67% of control (respectively) at 0.93% end-tidal halothane, somewhat more depression than we or Barash et al found. Interestingly Rathod et al found a statistically significant decrease in $LVID_d$ to 90% of control value at 0.93% end-tidal halothane. Their finding of lowered end-diastolic volume is in conflict with our results, those of Barash et al, and the invasive dog studies mentioned above, and remains unexplained. Perhaps the mode of ventilation employed is important. Rathod et al's subjects' control state was presumably during spontaneous respiration, while assisted respiration was employed during halothane administration. The present study employed controlled respiration throughout. Although the difference in $LVID_d$ between awake spontaneous and awake controlled respiration was not statistically significant, positive pressure respiration is well known to decrease venous return to the heart. This decreased venous return may have amplified the cardiac depressant effect of halothane thereby leading to ventricular dilation.

Routine application of echocardiography to study left ventricular function in the operating room is hampered by several factors. The equipment cost is high. The technique takes several weeks to learn. Obesity and increased anteroposterior chest diameter make the technique difficult, and sometimes preclude it. Patients with coronary artery disease may have dyskinetic areas visible to the echo beam causing errors in the performance variables. Patients with right ventricular volume overload may have paradoxically moving interventricular septa, precluding calculation of mean Vcf and percentage shortening.

Yet, the technique of echocardiography allows assessment of cardiac function that is both noninvasive and a direct measure of cardiac function as opposed, for example, to systolic time intervals, an indirect measure. Echocardiography might, therefore, be used in the differential diagnosis of, and response to treatment of cardiovascular problems during anesthesia. Although future technical refinements and automation would increase this potential, the halothane-induced cardiac depression found here serves to illustrate the potential anesthetic applications of echocardiography.

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ANESTH ANALG
58:30-32, 1979

Nitrous Oxide Increases Enflurane Concentrations Delivered by Ethrane Vaporizers

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NAWAF, K., AND STOELTING, R. K.: Nitrous oxide increases enflurane concentrations delivered by ethrane vaporizers. Anesth Analg 58:30-32, 1979.

Delivered enflurane concentrations from two calibrated Ethrane vaporizers were determined with total gas flows of 3, 5 and 8 L/min. Regardless of total gas flow the presence of 60% nitrous oxide increased enflurane concentrations by 20 to 40% above those concentrations present when only oxygen was flowing through the vaporizer. This nitrous oxide effect was present at all dial settings studied except the lowest engraved (0.25) concentration. Enflurane output at the 0.25% setting was 0.38% with or without nitrous oxide. Maximum changes in enflurane concentrations after adding nitrous oxide required about 5 minutes but the rapidity with which enflurane concentrations approached this maximum value were directly related to total gas flow. Similar effects of nitrous oxide on enflurane output from Cyprane Ethrane vaporizers were also measured.

The mechanism of increased vaporizer enflurane output in the presence of nitrous oxide is unknown but may reflect increased gas flow through the vaporizing chamber secondary to increase in gas density associated with nitrous oxide. A similar mechanism has been proposed to explain increased halothane concentrations delivered by Fluotec Mark 2 vaporizers in the presence of nitrous oxide.

Clinically, central nervous system stimulation and anesthetic overdose may occur from increased enflurane concentrations delivered when nitrous oxide is added to the gases flowing through the Ethrane vaporizer. The ability to deliver low enflurane concentrations is limited since the measured concentration at the lowest dial setting was nearly 0.4%.

Key Words: EQUIPMENT: vaporizers; ANESTHETICS, Volatile: enflurane; ANESTHETICS, Gases: nitrous oxide.

HALOTHANE concentrations delivered from Fluotec Mark 2 vaporizers are influenced by the composition of the gases flowing through the vaporizer.[1] For example, at the 0.5% vaporizer dial setting the halothane concentration was found to be 0.48% when the gas flow was 5 L/min of oxygen and 0.64% with 3 L/min of nitrous oxide and 2 L/min of oxygen. This increased halothane output was attributed to the greater density of nitrous oxide (1.96 gm/L) as compared with oxygen (1.43 gm/L) resulting in increased flow through the vaporizing chamber.

Gas mixtures of varying composition are stated not to influence concentrations delivered by the temperature compensated calibrated vaporizer (Ethrane-Ohio Medical Products) designed for use with enflurane (Ohio Medical Products brochure describing the calibrated vaporizer for use with Ethrane (enflurane)). However, the enflurane concentrations delivered by this vaporizer with or without nitrous oxide have not been reported. We sought to determine whether nitrous oxide influenced enflurane output from these Ethrane vaporizers.

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Methods

Two temperature-compensated Ethrane vaporizers (Ohio Medical Products) were evaluated using a Forreger anesthesia machine in a room maintained at 22 C. Enflurane concentrations during gas flows of 3, 5, and 8 L/min with and without about 60% nitrous oxide (i.e., 3 vs 2:1, 5 vs 3:2, and 8 vs 5:3) were measured at vaporizer dial settings designated 0.25, 0.50, 1, 2, 3, and 4%.

The order of dial settings and gas flows was varied. Glycerinized glass syringes were used to collect gas samples from the delivery tube of the anesthesia machine 10 minutes after initiating flow at each dial setting. The sampling site was 100 cm distal to the vaporizer outlet. These and subsequent gas samples were analyzed in duplicate for enflurane concentration by gas chromatography (flame ionization detector sensitive only to hydrocarbons, SE-30 on Chromosorb W). Peak height was converted to concentration in volumes percent by comparison with peak height produced by a known enflurane concentration. A known concentration of enflurane was prepared by adding 100 μl of liquid enflurane to each of four 2-L glass flasks. Details of this procedure have been previously described.[2] These standards were used to analyze enflurane concentrations delivered at the 0.25, 0.50 and 1% dial settings. Standards prepared using 250 μl of liquid enflurane were prepared to analyze concentrations delivered at dial settings of 2 and 3% while standards prepared with 400 μl were used for the 4% dial setting. The gas chromatograph was adjusted to make the known concentration read about 60% of full scale. Two standards were analyzed just before and after each vaporizer study period to ensure that gas chromatograph gain had not changed.

The time course of nitrous oxide effect on vaporizer enflurane output was determined in one of the two vaporizers. After 10 minutes of 3-L/min oxygen flow with the vaporizer dial setting at 1%, a gas sample was collected, the carrier gas flow then being changed to 2 L/min of nitrous oxide-1 L/min of oxygen. Samples for enflurane concentration were then collected for 10 minutes followed by samples for 10 minutes after returning to 3 L/min of oxygen.

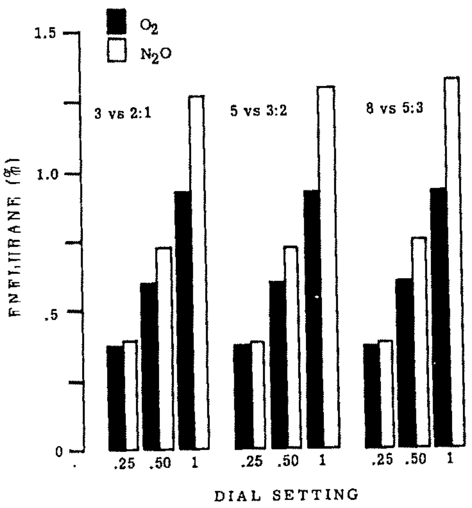

FIG 1. Enflurane concentrations delivered by a single vaporizer with or without nitrous oxide at gas flows of 3 vs. 2:1, 5 vs. 3:2, and 8 vs. 5:3 L/min and 0.25, 0.50, and 1% dial settings. Addition of nitrous oxide increased enflurane concentrations at all dial settings except .25%. The magnitude of increase was not influenced by total gas flow.

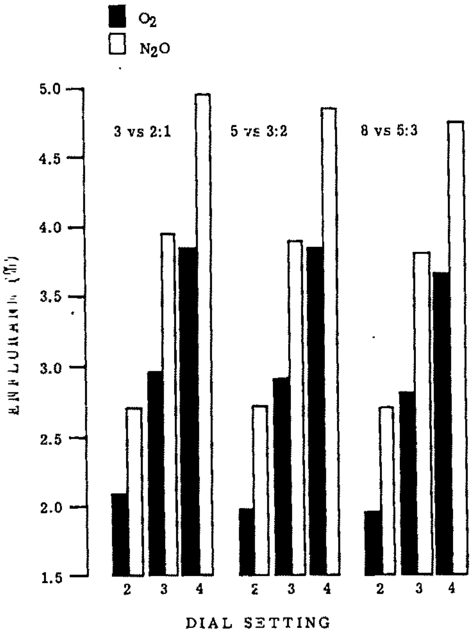

FIG 2. Enflurane concentrations continued from Fig 1 at 2, 3, and 4% dial settings. Nitrous oxide increased enflurane concentrations similar amounts at all dial settings regardless of total gas flow.

Results

Addition of 60% nitrous oxide at the 0.50, 1, 2, 3, and 4% dial settings increased enflurane output from both vaporizers similar amounts as compared with values obtained with oxygen alone (Figs 1 and 2). For example, at the 0.50 per cent dial setting enflurane concentration with 5 L/min of oxygen was 0.58% and 0.72% when the same total flow consisted of 60% nitrous oxide. When the dial setting was increased to 4% the enflurane concentration was 3.8% without and 4.9% with nitrous oxide. The magnitude of change in

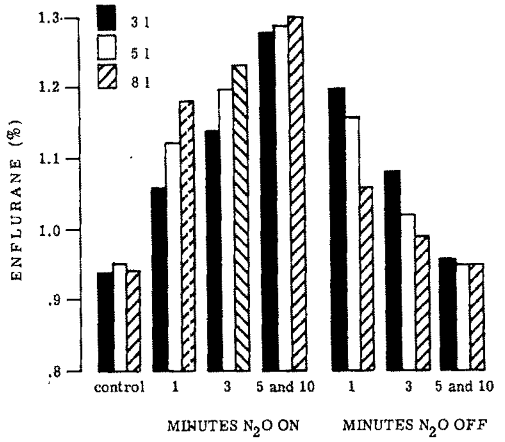

FIG 3. Enflurane concentrations delivered by a single vaporizer at the 1% dial setting. Control measurements are with 3, 5, or 8 L/min of oxygen followed by 10 minutes with 60% nitrous oxide at the same total gas flow and then a return to pure oxygen. Maximum effect of nitrous oxide on enflurane concentration was present after 5 minutes. The rapidity with which enflurane concentrations approached the maximum change produced by nitrous oxide and then returned to concentrations present before nitrous oxide was directly related to total gas flow.

enflurane concentration with the addition of nitrous oxide was similar with total gas flows of 3, 5, or 8 L/min. Nitrous oxide did not alter enflurane output at the 0.25 setting.

Increased enflurane concentrations were present 1 minute after changing the gas flow from oxygen to nitrous oxide plus oxygen (Fig 3). The enflurane concentration continued to increase until reaching the peak value 5 minutes after adding nitrous oxide. The rapidity with which enflurane concentrations approached the peak value was more rapid at the higher gas flows. Reduced enflurane concentrations were apparent 1 minute after replacing nitrous oxide with oxygen. The return to enflurane concentrations present before adding nitrous oxide required about 5 minutes. The rapidity with which enflurane concentrations decreased was directly related to the total gas flow.

Discussion

These data demonstrate that addition of nitrous oxide to the gas mixture flowing into the Ethrane vaporizer increased delivered enflurane concentrations 20 to 40% above the concentration present with oxygen alone at all dial settings above 0.25%. When the dial setting was 0.25% the measured enflurane concentration was 0.38% with or without nitrous oxide. The magnitude of increased enflurane output was not different with gas flows ranging from 3 to 8 L/min. However, the rapidity with which enflurane concentrations increased following the addition of nitrous oxide was directly related to total gas flow.

The mechanism by which nitrous oxide increases enflurane output from the tested vaporizers cannot be determined. However, the similarity of these data and the increased halothane concentrations delivered from Fluotec Mark 2 vaporizers in the presence of nitrous oxide suggests a common mechanism.[2] In Fluotec Mark 2 vaporizers halothane vapor produces a "back pressure" which must be overcome before flow into the vaporizing chamber can occur. More dense nitrous oxide increases the resistance to flow so pressure due to halothane vapor is more easily overcome. Thus, more flow enters the vaporizing chamber and resulting halothane output is increased. We speculate a similar mechanism is operating with the Ethrane vaporizers evaluated in this study.

We feel it is important to appreciate that enflurane output from these Ethrane vaporizers is increased when anesthetic machine gas flows contain nitrous oxide. For example, the presence of nitrous oxide at dial settings of 2, 3, and 4% increased enflurane concentrations about 1% above the indicated dial setting. Therefore, central nervous system stimulation described with high inspired enflurane concentrations would be more likely when nitrous oxide was present. For example, spike activity on the electroencephalogram increased in frequency when inspired enflurane was increased above 2%.[3] Our data show a delivered enflurane concentration of 2.7% at the 2% dial setting when 60% nitrous oxide is present. Anesthetic overdose is also more likely as emphasized by the fact that decreasing the dial setting from 3 to 2% and adding 60% nitrous oxide would result in little change in the enflurane concentration plus the added effect of nitrous oxide. Finally, the ability to deliver minimal enflurane concentrations is limited since the lowest concentration measured at the first engraved dial setting (0.25) was nearly 0.4 % with or without nitrous oxide.

Although not detailed in this report, we have measured similar effects of nitrous oxide on the enflurane output from Cyprane Ethrane vaporizers.

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ANESTH ANALG
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Management of Suspected Malignant Hyperpyrexia in an Infant

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FAUST, D. K., GERGIS, S. D., AND SOKOLL, M. D. Management of suspected malignant hyperpyrexia in an infant. Anesth Analg 58:33–35, 1979.

A case of possible malignant hyperthermia in a 6-month-old child is presented. Malignant hyperthermia was manifested in this patient by persistent metabolic acidosis in the intraoperative and postoperative periods, by a rapid rise in temperature with concomitant unresponsiveness in the postoperative period, and by a positive caffeine-halothane stimulation test. The malignant hyperthermia occurring in the postoperative period resolved promptly following administration of dantrolene sodium. An unusual aspect of this case is that both of the child's parents had normal CPK values and negative caffeine-halothane stimulation tests

Key Words: HYPERTHERMIA: Malignant pyrexia.

MALIGNANT hyperpyrexia (MH) has been reported in patients with a wide range in age. The youngest patient on record to have developed this syndrome was 14 months old.[1] We report on the perioperative management of a 6-month-old child with the potential for development of MH.

A 6-month-old, 7-kg white male presented with a rapidly enlarging soft tissue mass overlying the left angle of the mandible. Routine laboratory studies were normal except for elevated serum creatine phosphokinase (CPK) levels (370 and 376 units) on two occasions 5 days apart. In our laboratory, the upper level of normal for this age group is 200 units.[2] The hematocrit was 29%, the hemoglobin 9.8 gm/dl. The family history was negative for problems associated with anesthesia. Because of the possibility of malignancy in this rapidly enlarging mass we proceeded with anesthesia and surgery. However, the elevated levels of CPK led us to consider the child as a potential malignant hyperthermia patient and to conduct the anesthesia in such a manner as to minimize the risk of precipitating a pyrexic response.

The night before surgery an intravenous infusion was given to ensure adequate hydration and for use during anesthesia. Morphine (1 mg) and atropine (0.15 mg) were administered intramuscularly 45 minutes before induction of anesthesia. The operating room temperature was maintained at 20 C and the patient was placed on a cooling blanket. A bathtub with crushed ice and iced intravenous fluids were immediately available. Also immediately available were sodium bicarbonate, droperidol, procainamide, and dantrolene sodium. (The intravenous use of dantrolene sodium, an investigative drug, has been approved by the Human Research Committee of this hospital.)

A rapid smooth induction of anesthesia was achieved with fentanyl and thiopental and maintained with nitrous oxide-oxygen (60% and 40%, respectively) using a nonheated humidified nonrebreathing system with a flow rate of 5 L/min and later supplemented with thiopental and fentanyl. Endotracheal

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intubation was facilitated by the intravenous administration of 1 mg of pancuronium bromide. Respiration was manually controlled. The brachial artery was cannulated for pressure monitoring and blood gas sampling, and an additional intravenous line was inserted: Rectal, oral, and axillary temperatures were monitored using calibrated thermistor probes (Yellow Springs Instruments). Lead 2 of the electrocardiogram and precordial heart sounds were monitored. Thirty minutes after induction of anesthesia Pa$_{O_2}$ was 205 torr, Pa$_{CO_2}$ 26.7 torr, and pHa 7.369 with a base excess of −8.5 mEq/L. Arterial blood gases were repeated at 30-minute intervals during the 7½-hour procedure. Our suspicions concerning the possible development of MH were further aroused by the metabolic acidosis noted in the first arterial blood sample and were sustained when the second set of blood gases revealed a Pa$_{O_2}$ of 166 torr, a Pa$_{CO_2}$ of 35.1 torr, a pHa of 7.25, and a base excess of −11 mEq/L. The oral temperature was 36.4 C. Metabolic acidosis has been reported by Gronert et al[3] as a sign of malignant hyperpyrexia. At this point 5 mEq of sodium bicarbonate were administered. The metabolic acidosis continued and required a total of 15 mEq of sodium bicarbonate administered in 5-mEq increments during the procedure to correct the acidosis. Approximately 3 hours after induction of anesthesia the patient's temperature rose from 36.5 to 37.6 C over a 40-minute period. This was associated with an increase of pulse rate from its steady rate of 130 up to 160 beats per minute. Droperidol (2.5 mg) was administered intravenously and the patient was cooled to 36 C by lowering the temperature of the blanket and by application of ice packs to the groin. During the operation a biopsy of the sternocleidomastoid muscle was taken and immediately subjected to a caffeine-halothane challenge test.[4] The result of this test was positive for susceptibility to MH (Figure). No microscopic examination of the muscle was conducted. At the end of the operation the patient was taken to the recovery room with the endotracheal tube in place, and the patient was spontaneously breathing a Fi$_{O_2}$ of 0.4 and had a temperature of 37 C. Blood gas analysis revealed a Pa$_{O_2}$ 101.5 torr, Pa$_{CO_2}$ of 25.4 torr, and pHa of 7.33. This metabolic acidosis persisted but the patient otherwise appeared to be doing well and was discharged to the ward the following morning with a rectal temperature of 37.5 C and blood gases of Pa$_{O_2}$ of 82.8 torr, Pa$_{CO_2}$ 28 torr, pHa of 7.39 and a base excess of −6.7 mEq/L while spontaneously breathing room air. Approximately 3 hours after leaving the recovery room the patient's rectal temperture rose from 37.6 to 39.0 C despite the use of a cooling blanket. Droperidol (1.6 mg) was administered intravenously along with 7 mg dantrolene orally, and the patient was transferred to the recovery room for closer observation. The child became progressively less responsive and arterial blood gases showed the Pa$_{O_2}$ to be 99 torr, the Pa$_{CO_2}$ 18.2 torr, and the pHa 7.27. The patient was given 18 mEq of sodium bicarbonate and 50 mg of dantrolene sodium intravenously. Over the following 20 minutes the temperature returned to 37 C, at which time blood gas analysis revealed a Pa$_{O_2}$ of 76.8 torr, Pa$_{CO_2}$ of 31 torr, pHa of 7.42, and base excess of −8.28 mEq/L. Concomitant with this the patient's mental status markedly improved although he was still slightly less responsive than he had been earlier in the day.

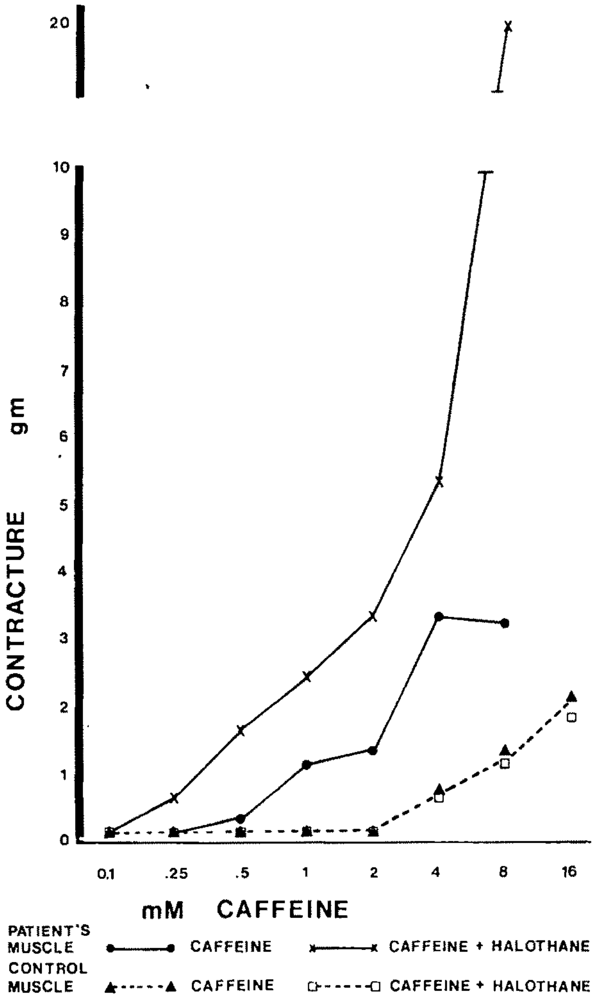

FIGURE. Response of the patient's sternocleidomastoid muscle biopsy to caffeine and halothane compared to a normal response. Contracture at low concentrations and steep slope indicate the patient's susceptibility to MH.

On two later occasions over the next 36 hours the patient's temperature transiently rose to 38.5 C. These elevations responded promptly to usual external cooling measures. The metabolic acidosis was treated with bicarbonate on two further occasions over this same period. The patient was seen by a pediatric neurologist whose impression was that of malignant hyperpyrexia, principally by exclusion of other disease processes. The patient was discharged from the recovery room on the 4th postoperative day and has done well since; 48 and 72 hours postoperatively serum CPK levels were 488 and 237 units, respectively.

Histologically the tumor was a proliferative parotid hemangioma.

Both parents had normal serum CPK levels on two separate occasions and vastus lateralis muscle biopsies showed normal responses to caffeine-halothane stimulation. This suggests the possibility of a spontaneous mutation in this child.[5] More likely, however, it represents the variable penetrance[6] characteristic of the inheritance pattern of malignant hyperpyrexia. The patient is an only child.

ACKNOWLEDGMENT

Dantrolene sodium, lyophilized for intravenous use, was kindly supplied by Eaton Laboratories.

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Meperidine Pharmacokinetics

Meperidine pharmacokinetics in the maternal-fetal unit were evaluated by use of the chronic pregnant ewe preparation. After maternal administration (2.5 mg/kg IV), meperidine appears in fetal plasma within 2 minutes at a level approaching that in maternal plasma. Fetal and maternal blood levels decline at a similar rate. Compared to the IV dose kinetics, the rate and amount of meperidine transferred from mother to fetus is decreased after intramuscular administration. After the administration of normeperidine to the mother, fetal normeperidine plasma levels peak at 5 minutes and decline at a slower rate than maternal levels. When meperidine is administered IV to the fetus, the drug appears in maternal plasma within 2 minutes and peaks at 5 minutes. At a continuous infusion of meperidine (0.06 mg/kg/min) to the mother, steady state is achieved in both maternal and fetal plasma within 60 minutes. At steady state, the fetal/maternal plasma meperidine concentration ratio is equal to 0.30. When differences between maternal and fetal plasma protein binding and degree of ionization are taken into account the recalculated steady-state concentration ratio is 0.38. The authors propose that meperidine confers on the maternal-fetal unit the characteristics of a two-compartment open model with elimination from both maternal and fetal compartments. This model suggests that the elimination by the fetus makes an important contribution to the disposition of meperidine. (*Szeto HH, Mann LI, Bhakthavathesalan A, et al: Meperidine pharmacokinetics in the maternal-fetal unit. J Pharmacol Exp Ther 206:448–459, 1978*)

ANESTH ANALG
58:36-39, 1979

Failure of Naloxone and Naltrexone to Antagonize Halothane Anesthesia in the Dog

Nathan L. Pace, MD,* and K. C. Wong, MD, PhD†

PACE, N. L., AND WONG, K. C.: Failure of naloxone and naltrexone to antagonize halothane anesthesia in the dog. Anesth Analg 58:36–39, 1979.

The effects of two narcotic antagonists, naloxone and naltrexone, on minimum alveolar anesthetic concentration (MAC) were studied during halothane anesthesia in the dog. Following induction of anesthesia, MAC was determined in duplicate. Each dog was then given one of the two narcotic antagonists and MAC was redetermined in duplicate: five dogs were given naloxone, 3 mg/kg IV, followed by an intravenous infusion of naloxone, 0.025 mg/kg/min; five dogs received naltrexone, 5 mg/kg IV. MAC was unaffected by the narcotic antagonists. Failure of narcotic antagonists to reverse halothane anesthesia suggests that the endogenous opioid peptides are not involved in the anesthetic state produced by halothane.

Key Words: ANTAGONISTS, Narcotic: naloxone; ANTAGONISTS, Narcotic: naltrexone; ANESTHETICS, Volatile: halothane.

HIGHLY specific opiate receptors on neuronal membranes have recently been discovered in the brain.[1] A further search has revealed endogenous polypeptides which bind to these opiate receptors.[2, 3] These peptides, which have now been synthesized and shown to be morphinomimetic when administered to animals,[4] are referred to as opioid peptides or endorphins; a subgroup of opioid peptides, the pentapeptides are known as enkephalins. The pure narcotic antagonist naloxone appears to reverse all effects of exogenously administered endorphin. The neurochemical role of the large polypeptide endorphins is unclear, though considerable evidence suggests enkephalins may have a role as a neurotransmitter.[5]

The existence of endorphins or enkephalins with a neurophysiologic role would demand that direct pharmacologic actions of a pure narcotic antagonist be seen. Yet traditionally, the pure narcotic antagonist naloxone has been considered to have no important direct effects of its own, except to antagonize the actions of exogenous opioid drugs.[5] Another possibility must be considered; perhaps certain appropriate circumstances must be imposed on the experimental subject to activate the endogenous opioid system before a clear direct action of naloxone could be expected. The role of opioid peptides in narcotic addiction,[6] mental illness,[7] pain states,[8, 9] temperature regulation,[10] and acupuncture analgesia[11] is currently being investigated. As mentioned above, these studies postulate that certain pathologic and/or experimental conditions activate the endorphin system; pharmacologic activity of naloxone under these conditions is taken as evidence of endorphin activity.

This reasoning has been applied to studies of general anesthesia. A recent report indicates that naloxone reverses nitrous oxide (N_2O) analgesia in mice (N_2O was given in concentrations sufficient to produce analgesia, not anesthesia).[12] Antagonism of gen-

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Address reprint requests to Nathan L. Pace, MD.

eral anesthesia (cyclopropane, halothane, and enflurane) by naloxone has also been reported in the rat,[13] as has elevation of halothane minimum alveolar anesthetic concentration (MAC) in the dog by naloxone (Yong HH, Shiwaku Y, Derry A, et al: Effects of chronic morphine addiction and naloxone on halothane MAC in dogs. In Abstracts of Scientific Papers, American Society of Anesthesiologists 1977 Annual Meeting, New Orleans, Louisiana, pp 737–738). The objective of this study was to seek any change in halothane MAC in dogs when given large doses of either of two pure narcotic antagonists, naloxone or naltrexone (a more potent cyclopropyl derivative of naloxone).[14]

Methods

The determination of MAC followed the method of Eger.[15] Mongrel dogs unselected for age and weighing about 10 kg (11.8 ± 1.9 kg, mean ± SD) were anesthetized with halothane in oxygen. Without the use of muscle relaxants or other drugs, the trachea was intubated with a tightly fitting, cuffed endotracheal tube. Anesthesia was continued and the dogs mechanically ventilated to maintain arterial P_{CO_2} about 25 to 30 torr; the anesthetic system also allowed spontaneous respiration. A femoral arterial catheter was inserted for arterial blood gas sampling and continuous pressure monitoring. A foreleg vein was cannulated for drug and fluid administration. Rectal temperature was taken with a glass thermometer and temperature maintained between 37–38 C with heating lamp and blanket.

Respiratory gases were aspirated from a catheter inserted down the endotracheal tube and monitored continuously on two infrared gas analyzers (Beckman LB-2) for halothane and carbon dioxide; the infrared analyzers were calibrated every 2 hours against known concentrations of these gases. A given end-tidal anesthetic concentration was maintained for at least 15 minutes prior to testing. The stimulus used was a 25-cm hemostat clamped on the shaved tail 5 to 10 cm from its base until the rachet caught; the tail was moved continuously with the hemostat for 60 seconds. Gross, purposeful, muscular movements (jerking, twisting, running, or clawing) were considered a positive response; coughing, swallowing, chewing, stiffening, and hyperventilation were not considered positive responses.[15] MAC was taken to be the concentration midway between the highest concentration allowing and the lowest concentration preventing a positive response. MAC was determined in duplicate; the time required for each determination was about 1 hour. MAC was expressed as a fractional concentration of one atmosphere (760 torr)

After the control determination of MAC in duplicate in each dog, MAC was redetermined in duplicate under the following conditions. In five dogs receiving naloxone, 3 mg/kg IV, was given over a few seconds followed by a naloxone infusion of 0.025 mg/kg/min. In five dogs receiving naltrexone, 5 mg/kg IV, was given over a few seconds. The first MAC determination was completed about 1 hour following injection; another hour allowed a second determination.

Change in MAC after the narcotic antagonist was evaluated by a two-way analysis of variance (ANOVA).[16] The control MAC values of dogs receiving naloxone and naltrexone were compared by a two-level nested one-way ANOVA.[16] The test stastistic for an ANOVA is expressed as the variance ratio $F_{(v_1, v_2)}$ where v_1 and v_2 are the degrees of freedom of the numerator and denominator. The control MAC for both groups was compared with previous dog MAC data by an unpaired *t*-test; *p* values less than 0.05 were considered statistically significant.

Results

The results are given in the Table. There was no effect of narcotic antagonists on halothane MAC. The dogs were observed closely for signs of light anesthesia immediately following the administration of naloxone or naltrexone (tachycardia, hypertension, tachypnea, movement, coughing, swallowing, chewing, stiffening); no changes were observed except for transient (30 seconds), mild hypotension following naltrexone. There was no difference between the control MAC of the dogs which received naloxone and those which received naltrexone ($F_{(1, 8)} = 1.77$; $p > 0.2$). The combined control MAC for the two groups (0.96 ± 0.07; mean ± SEM) is not different from the

TABLE

Effect of Narcotic Antagonists on Halothane MAC (% atm; mean ± SEM)

	Control	Antagonist
Naloxone 3 mg/kg IV + 0.025 mg/kg/min IV	0.87 ± 0.11	0.85 ± 0.08
(n = 5)	$F_{(1, 10)} = 0.42$; $p > 0.2$	
Naltrexone 5 mg/kg IV	1.05 ± 0.07	0.98 ± 0.05
(n = 5)	$F_{(1, 10)} = 2.93$; $p > 0.2$	

accepted halothane MAC for dogs (0.87 ± 0.02; mean ± SEM) [$t = 1.59$ (df = 34), $p > 0.1$].[17]

Discussion

These results demonstrate no antagonism of the anesthetic actions of halothane by naloxone or its derivative naltrexone; these results do not support the reports suggesting a role for the endorphins in the anesthetic state (Yong HH, Shiwaku Y, Deery A, et al: Effects of chronic morphine addiction and naloxone on halothane MAC in dogs. In Abstracts of Scientific Papers, American Society of Anesthesiologists 1977 Annual Meeting, New Orleans, Louisiana, pp 737–738).[12, 13] Our results support those of others who have similarly been unable to demonstrate antagonism of halothane or nitrous oxide by naloxone.[18–20]

There are several possible explanations of our results.

It has been noted that MAC is only one point on the dose-response relationship between anesthetic concentration and depth of anesthesia.[21] Conceivably, the reversal of an endorphin effect by naloxone could alter the shape of the anesthetic dose-response curve without changing MAC. This possibility cannot be excluded by our study.

The absence of anesthesia reversal is not from lack of endorphins in dog brain. Endorphins have been found in all vertebrates studied including dog.[22] On the other hand, it has been suggested that there is a diurnal rhythmicity in the activity of the endorphins.[23] Whether this could obscure an interaction between anesthetic and endorphin during the approximately 4 to 6 hours required for the study is unknown.

As the dog has not previously been used in studies of a putative neurochemical role of endorphins and enkephalins, the appropriate dose of antagonist is not well defined. The doses of antagonists used in this study are of the same magnitude as used in other species. In addition, following the 3 mg/kg of naloxone bolus, we infused a further 3 mg/kg of naloxone over the 2 hours necessary to determine MAC in duplicate. The kinetics of naloxone and naltrexone in rat brain[24, 25] and the relative affinities of these antagonists for enkephalin receptors in the brain[26] indicate that even 2 hours after the administration of naloxone, 3 mg/kg IV, or naltrexone, 5 mg/kg IV, in the rat, there would still remain sufficient antagonist to inhibit enkephalin at brain receptors. From recent work in our laboratories showing serum naloxone and naltrexone kinetics to be quite similar in the rat and in the dog[27] and assuming that naloxone and naltrexone affinities in dog brain are not dissimilar from those in the rat, then there should have been a sufficient brain antagonist concentration throughout the 2 hours required to determine MAC.

Our results do not suggest any role for endorphins in the anesthetic state produced by halothane.

ACKNOWLEDGMENT

The authors thank Dr. Ralph Jacobsen of Endo Laboratories for the generous supply of naloxone HCl and naltrexone HCl.

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Myocardial Reinfarction after Anesthesia and Surgery

During the years 1974 and 1975 at the Mayo Clinic, 587 patients who had suffered previous myocardial infarctions underwent anesthesia and surgery. Thirty-six (6.1%) had a reinfarction and 25 (69%) died. Patients operated on within 3 months of the previous infarction had a 27% reinfarction rate. This decreased to 11% if the infarct had occurred 3 to 6 months previously and stabilized at 4 to 5% if the interval was more than 6 months. Risk factors associated with significantly increased reinfarction rates included preoperative hypertension, intraoperative hypotensive episodes, and noncardiac thoracic or upper abdominal operations of more than 3 hours duration. Time under anesthesia was srikingly correlated with reinfarction rates in the entire group. Postoperative intensive care unit admission did not significantly affect the reinfarction rate, nor did diabetes, angina, patient age or sex, or site of the previous myocardial infarction. *(Steen PA, Tinker JH, Tarhan S: Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566–2570, 1978)*

Hypotension after Use of Plasma Protein Fraction

Thirteen lots of plasma protein fraction made by one manufacturer were implicated in 23 recent reports of hypotension in surgical patients. Four of these patients required resuscitation after rapid administration of the product in the postoperative period. All implicated lots had prekallikrein-activator activity but low levels of bradykinin and kallikrein. The prekallikrein activator was identified as Hageman-factor fragments by molecular weight, isoelectric point and inhibition by antibody to Hageman factor. These data suggest that Hageman-factor fragments are potent hypotensive agents, presumably because they trigger the generation of bradykinin in recipients. Prekallikrein-activator activity, usually at levels lower than those in the initial 13 implicated lots, was frequently detected in plasma protein fraction made by other manufacturers. Several of these lots were associated with additional reports of hypotension. Prekallikrein-activator activity rarely occurred in albumin. *See Also*—Editorial. Colman RW: Paradoxical hypotension after volume expansion with plasma protein fraction. N Engl J Med 299:97–98, 1978. (*Alving BM, Hojima Y, Pisano JJ, et al: Hypotension associated with prekallikrein activator (Hageman-factor fragments) in plasma protein fraction. N Engl J Med 299:66–70, 1978*)

ANESTH ANALG
58:40-41, 1979

Cardiovascular and Pulmonary Responses following Etomidate Induction of Anesthesia in Patients with Demonstrated Cardiac Disease

John M. Gooding, DO, Jen-Tsoh Weng, MD, PhD, Robert A. Smith, RRT, Gary T. Berninger, RRT, and Robert R. Kirby, MD

GOODING, J. M., WENG, J.-T., SMITH, R. A., BERNINGER, G. T., AND KIRBY, R. R.: Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. Anesth Analg 58:40–41, 1979.

Cardiovascular and pulmonary effects following the administration of 0.3 mg/kg of etomidate were studied in patients with documented cardiac disease. The only significant change was a slight elevation (2 torr) in arterial carbon dioxide tension.

Key Words: ANESTHETICS, Intravenous: etomidate; INDUCTION, Anesthetic: etomidate.

AN intravenous drug that produces rapid onset of hypnosis without adverse effects on the respiratory and cardiovascular systems would be appreciated by anesthesiologists. Such a drug would fill an existing gap in our current armanentarium of anesthetic induction agents. Previous reports have suggested that etomidate, a new rapid acting nonbarbiturate hypnotic, lacks significant adverse cardiovascular and respiratory effects.[1-8] However, these studies did not include patients with preexisting cardiovascular disease.

In order to assess the cardiovascular and respiratory effects of etomidate in high risk patients we undertook such a study in surgical patients with demonstrated cardiac disease.

Materials and Methods

Twenty-two patients (18 men and four women, mean age 55 ± 9 years), A.S.A. classes III and IV, were studied. (Approval for the study was given by the Use of Human Subjects Committee at Tulane University School of Medicine. Informed consent was obtained from each subject.) All had existing cardiac disease documented by prior catheterization. Two patients were scheduled for peripheral vascular surgery, eight for valvular heart surgery, and 12 for coronary artery bypass grafting. Premedication consisted of 5 mg of droperidol 1 hour prior to anesthetic induction in every patient. Balloon flotation, thermistor-tipped, pulmonary artery catheters as well as radial artery catheters were inserted percutaneously. Control measurements of heart rate (HR), mean arterial pressure ($\overline{AP}$), central venous pressure (CVP), mean pulmonary artery pressure ($\overline{PAP}$), pulmonary artery occlusion pressure (PAOP), cardiac output (CO), and arterial and mixed venous blood gas tensions were obtained. Etomidate was then injected intravenously in a dose of 0.3 mg/kg in 60 seconds. Oxygen was administered preceding and during the induction period. The above measurements were repeated between 1 and 3 minutes following etomidate

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TABLE

Effect of Etomidate on Cardiac and Pulmonary Variables (n = 22)*

	Before etomidate	After etomidate
HR	69 ± 12	70 ± 9
$\overline{\text{AP}}$ (torr)	91 ± 18	88 ± 21
CVP (torr)	6 ± 5	7 ± 4
$\overline{\text{PAP}}$ (torr)	20 ± 5	20 ± 5
PAOP (torr)	14 ± 5	15 ± 5
CI ($L \cdot min^{-1} \cdot m^{2-2}$)	2.6 ± 0.7	2.7 ± 0.6
Pa_{O_2} (torr)	290 ± 68	292 ± 70
Pa_{CO_2} (torr)	41 ± 4	43 ± 5†
$C(a - \bar{v})_{O_2}$ (ml %)	4.6 ± 1	4.7 ± 1
$\dot{Q}_{sp}/\dot{Q}_t$ (%)	21 ± 0.05	21 ± 0.05

* Values are means ± SD. See text for abbreviations.

† $p < 0.05$.

injection. Using the above data and body surface area, cardiac index (CI), arteriovenous oxygen content difference ($C(a-\bar{v})O_2$), and total intrapulmonary shunt ($\dot{Q}_{sp}/\dot{Q}_t$) were calculated.

Results

Due to rapid onset and brief duration of action of etomidate (at a dose of 0.3 mg/kg, sleep is produced in a single arm-brain circulation time and inactive metabolites peak by 7 minutes[6, 9]), it was elected to obtain data between 1 and 3 minutes following injection. A slight elevation of arterial carbon dioxide tension (Pa_{CO_2}) was the only change of statistical significance (Table); however, this change was not clinically remarkable. Some patients tended to develop upper airway obstruction indicated by episodes of snoring. No other consistent effects on respiration were noted.

Discussion

Hemodynamic stability was observed following the administration of 0.3 mg/kg of etomidate in patients at risk because of cardiac disease. The slight elevation in heart rate reported in previous studies of noncardiac patients[1, 3, 4] did not occur in our patients. This may be due to the reduced incidence of venous pain on injection with the new, less acidic (pH 5.0) solution[10] that was used in our patients. The stability of cardiovascular function suggests a lack of significant effects on either the peripheral and pulmonary vascular beds or on the myocardium itself. Absence of appreciable changes in arterial blood gases confirms previous findings.[3] Total intrapulmonary shunt was not altered and suggests a role for etomidate in anesthetizing patients with respiratory insufficiency and/or preexisting intrapulmonary shunting.

Cardiovascular stability in our study of high risk cardiac patients corroborates previous findings in noncardiac patients. Alterations in arterial blood gas tensions or total intrapulmonary shunt did not occur. In patients at risk because of heart disease it would appear that etomidate would provide a greater margin of safety during the induction of anesthesia than the ultrashort-acting barbiturates which produce vascular dilation, adversely affect cardiac output, and depress respiration.

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ANESTH ANALG
58:42–48, 1979

Hypotension and Respiratory Distress Caused by Rapid Infusion of Mannitol or Hypertonic Saline

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STIFF, J. L., MUNCH, D. F., AND BROMBERGER-BARNEA, B.: Hypotension and respiratory distress caused by rapid infusion of mannitol or hypertonic saline. Anesth Analg 58:42–48, 1979.

Following a case of mannitol-induced respiratory and circulatory collapse, the effects of hyperosmolar injections on pulmonary arterial pressure, systemic blood pressure, and cardiac output were studied in dogs. The injection of 20 ml of 10% NaCl into the pulmonary artery increased pulmonary arterial pressure and decreased systemic blood pressure by approximately 50% of control values. Injections of solutions of equal hyperosmolar strength, 50 ml of 25% mannitol or 50 ml of 4% NaCl into the pulmonary artery produced no significant elevation of pulmonary arterial pressure, but were associated with comparable decreases in systemic blood pressure. When allowed to vary, cardiac output increased with injections of all three hyperosmolar solutions, yet was still accompanied by falls in systemic blood pressure as large as when cardiac output was held constant. Vagotomy did not prevent these changes in systemic and pulmonary arterial pressure, nor the increase in cardiac output. After five to 10 injections, the decreases in systemic blood pressure with any of the solutions and the increases in pulmonary arterial pressure with 10% NaCl disappeared and further injections were without effect. It is concluded that administration of mannitol probably does not cause pulmonary edema due to fluid overload, nor does it cause heart failure as evidenced by increases in pulmonary arterial pressure. However, rapid injection may cause a fall in blood pressure and may on occasion be accompanied by bronchospasm, especially in sensitive subjects.

Key Words: FLUID BALANCE: hypertonic solutions; BLOOD PRESSURE: hypertonic solutions and.

THE administration of mannitol to reduce cerebral spinal fluid pressure, cerebral edema, or introcular pressure, as well as prophylaxis against oliguria[1] has been associated on occasion with the onset of labored breathing. The mechanism responsible for such respiratory distress is unclear. Cautions against rapid administration of the drug usually state that the increase in blood volume could lead to fluid overload and pulmonary edema.[2, 3] However, Barry and Berman[4] observed no circulatory overload in 150 patients who received mannitol, including patients with severe heart disease. Morgan et al[5] in their series of patients with aspirin and barbiturate overdoses used large amounts of mannitol and noted pulmonary edema in only one case, an anuric patient who received 1081 mg.

Spaeth et al[6] reported a case of anaphylactic reaction characterized by severe respiratory distress following mannitol administration. The case presented here is similar.

Case Report. A 61-year-old male was admitted for

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cataract extraction. He had asthma for many years, and at the time of admission his asthma was controlled on oxtriphylline, prednisone, beclomethasone, and metaproterenol. He had no other significant medical history and no evidence of heart disease. On the morning of the scheduled operation an intravenous infusion with mannitol (20%) was started to reduce intraocular pressure. Within a few minutes he complained of a choking sensation. By the time 40 ml had been infused he complained of extreme shortness of breath and became cyanotic. The infusion was stopped; however, he lost consciousness, became apneic, and required endotracheal intubation and ventilatory support. He was transferred to the intensive care unit and mechanically ventilated, and an intravenous aminophylline infusion was begun. After 2 hours he resumed adequate spontaneous ventilation. He was extubated after 4 hours and made an uneventful recovery. Following his discharge from the hospital studies (Lichtenstein LM: Personal communication, 1978) showed that his circulating basophils released histamine in response to hyperosmolar challenge in larger amounts than other subjects studied.

The case resembles that presented by Spaeth et al[6] in that the reaction occurred almost immediately upon the start of mannitol infusion in a patient without factors which might predispose to development of pulmonary edema but with a history of asthma, although in the case of Spaeth et al the asthma was no longer active.

To significantly increase blood volume by mannitol would require a greater volume than was given to our patient. Therefore, it is unlikely that circulatory overload leading to pulmonary edema was a factor. How-

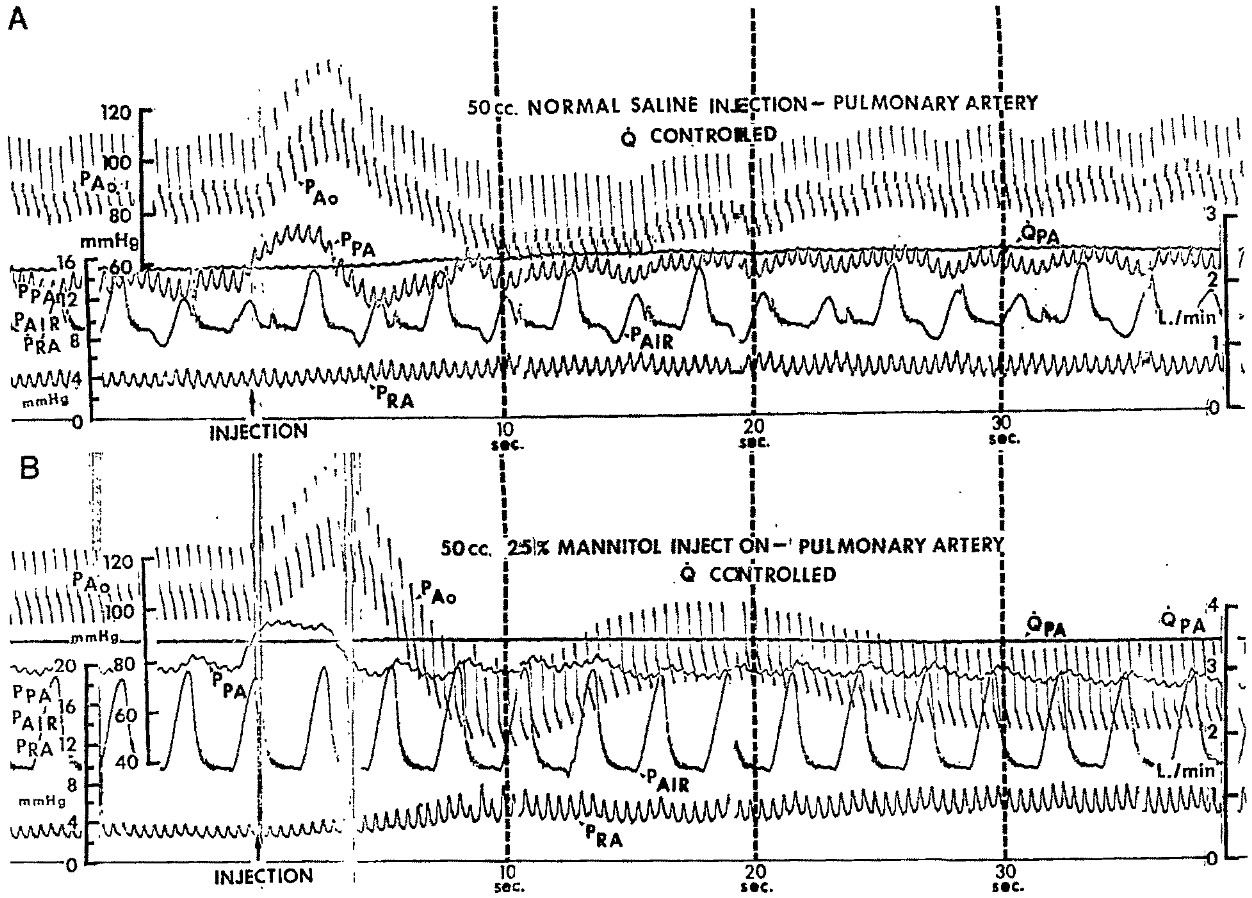

FIG 1. *A*, Record of a control injection of 50 ml of isotonic saline solution: P_{Ao}, aortic pressure; P_{PA}, pulmonary artery pressure; P_{RA}, right atrial pressure; P_{AIR}, airway pressure; Q_{PA}, total pulmonary blood flow. All pressures are in millimeters of mercury; arrow marks time of injection. Note: injection artifact consists of rapid rise in P_{Ao} and P_{PA} which has largely disappeared after 10 seconds and is followed by a short hypotensive rebound stage. By the time 20 seconds have elapsed, everything is back to control values. *B*, Traces and symbols as before; however, while injection artifacts are similar, response to hyperosmolar mannitol injection shows fall in systemic blood pressure which is sustained beyond 40 seconds. Cardiac output, i.e., pulmonary blood flow, was kept constant throughout.

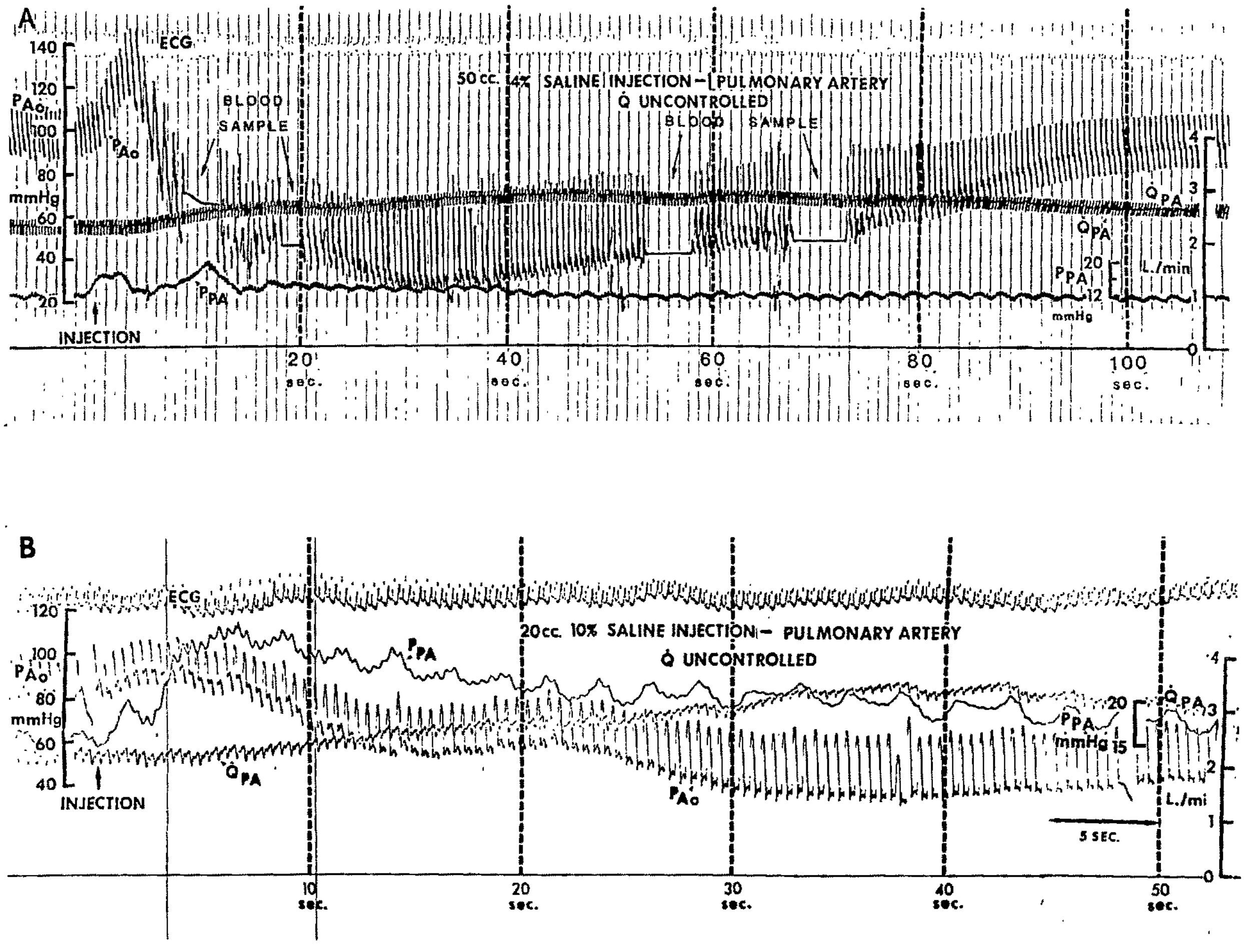

FIG 2. Traces as in Fig 1. Cardiac output is not being controlled and shows an increase in response to injection of 4% saline (*A*) and 10% saline (*B*). Since amount injected in *B* was only 20 ml the injection artifact was much smaller than in *A* but the fall in systemic pressure is almost 50% in both cases. In addition, note the immediate rise in P_{PA} which still remains elevated after 50 seconds.

ever, it has been shown experimentally that rapid infusion of hypertonic solutions other than mannitol may lead to rapid and substantial increases in pulmonary arterial pressures.[7-11] To determine whether rapid infusion of mannitol could lead to heart failure as evidenced by increases in pulmonary arterial pressure we studied the circulatory effects of mannitol and hypertonic saline in dogs under conditions in which cardiac output could either be held constant or allowed to vary.

Methods

Six mongrel dogs (15 to 25 kg each) were anesthetized with intravenous sodium pentobarbital (30 mg/kg), endotracheally intubated, and ventilated with a Harvard respirator. The dogs were given heparin, and a midsternal thoracotomy was performed. Catheters were advanced into the aorta, left atrium, pulmonary artery, right atrium, and femoral vein to record pressures. The dogs were placed on a right heart bypass system previously described.[12] In this preparation all venous return entering the right atrium is drained and pumped directly into the pulmonary artery. Thus pulmonary blood flow, i.e., total cardiac output, can be controlled or left uncontrolled as desired. Pulmonary blood flow was continuously recorded with an electromagnetic flow probe.

Isotonic control solutions consisted of 50 ml of 0.9% NaCl or 50 ml of autologous blood. Hypertonic solutions used were 50 ml of 25% mannitol (68 mosmol/50 ml), 20 ml of 10% NaCl (69 mosmol/20 ml), or 50 ml of 4% NaCl (69 mosmol/50 ml). Solutions were injected manually into either the pulmonary artery or a femoral vein. Injection time was 3 to 5 seconds which produced an artifact on the pressure trace which was generally over within 10 seconds. In three experiments femoral venous injections were tried as well as pulmonary artery injections, because clinically mannitol is given intravenously and in order to help locate site of action of hyperosmolar solutions. Femoral injection produced a longer time delay before any pressure responses were observed because of the extra corporeal tubing and pump system.

In five experiments the vagal nerves were bisected bilaterally after initial injections of control and hyperosmolar injections following which injections of hyperosmolar solutions were then repeated. Vagotomies were performed in order to determine whether the decrease in systemic pressure and the rise in pulmonary artery pressure with 10% saline could be abolished. The order in which substances were injected was chosen at random. In each experiment, pressures, total pulmonary blood flow, and ECG were recorded before, during, and after each injection until all traces returned to control levels. Variables continuously recorded included: aortic pressure (P_{Ao}), pulmonary artery pressure (P_{PA}), right atrial pressure (P_{RA}), left atrial pressure (P_{LA}), and airway pressure (P_{AIR}). Mean aortic pressure was calculated by the equation $P_{Ao\ mean} = P_{Ao\ diast} + \frac{1}{3}(P_{Ao\ syst} - P_{Ao\ diast})$. Mean pressures are reported unless stated otherwise. Since cardiac output increased in all uncontrolled conditions and this increase would have to cause a rise in systolic pressure, the mean pressure actually underestimates the magnitude of the fall in systemic vascular resistance which is produced by the hyperosmolar injections. When, after repeated injections, the systemic depressor responses disappeared, the ability of the peripheral arteriolar bed to dilate was tested on several occasions by injection of 400 to 1200 μg of acetylcholine into the aorta.

Results

Fig 1 shows representative tracings comparing rapid pulmonary arterial injections of 50 ml of isotonic NaCl (0.9%) with 50 ml of 25% mannitol in the same dog. With both solutions there was an injection artifact consisting of a transient 3 to 4 mmHg rise in pulmonary arterial pressure and a corresponding 20 mmHg rise in systemic blood pressure followed by a momentary stretch relaxation response. The systemic

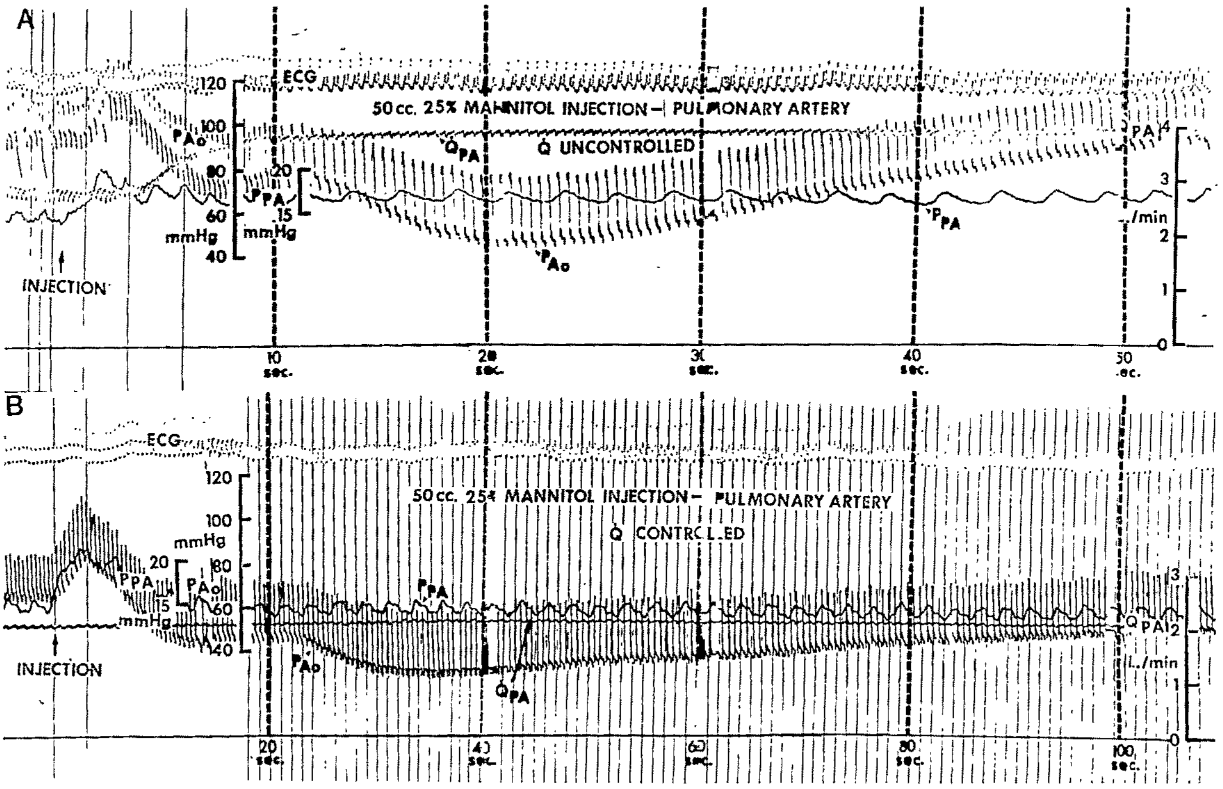

FIG 3. Traces as before. Control of pulmonary blood flow, i.e., cardiac output, has little or no effect on magnitude of blood pressure fall produced by mannitol. *A* was recorded at twice the paper speed of *B*. Cardiac output in *A* increased while in *B* it was controlled and remained unchanged.

blood pressure rapidly returned to the preinjection level following isotonic saline as well as after autologous blood but remained lower following hypertonic mannitol.

Rapid pulmonary arterial injections of 50 ml of 4% NaCl and 20 ml of 10% NaCl are shown in Fig 2. The 4% NaCl showed a similar injection artifact as described for Fig 1. However, the rise in pulmonary arterial pressure following 20 ml of 10% NaCl was much greater and more sustained and cannot be explained by the introduction of volume alone especially since the volume injected was less (20 ml). Both hypertonic salt solutions produced sustained falls in systemic pressure as did 25% mannitol (Fig 1). The hypotensive response was not due to a decrease in cardiac output, which was held constant, and when we allowed cardiac output to vary it increased with all injections of hypertonic solutions (Fig 3). Vagotomy caused no change in the response of pulmonary arterial or systemic pressure (Fig 4) to the injection of hyperosmolar solutions.

Rapid femoral vein injections, as shown in Fig 5, did not cause the injection artifact seen with pulmonary arterial injection, but the sustained decrease in systemic blood pressure occurred. The onset of the fall was delayed since the injectate had to go through the bypass system before reaching the pulmonary artery and then the systemic vascular bed.

The response to hyperosmolar injection was reproducible in each animal only about five to 10 times; after that, further injections caused only an injection artifact but no sustained fall in systemic blood pressure. Progressive decrease in this responsiveness is shown in Fig 6, which plots the magnitude of decrease in systemic pressure as a function of the number of hyperosmolar injections in all dogs. When no further response could be elicited in two dogs, injections of 400 to 1200 μg of acetycholine into the aorta caused an immediate drop in systemic blood pressure, demonstrating that the systemic vascular bed was still capable of vasodilation.

There was no significant increase in left atrial pressure in any of the experiments.

Discussion

Pulmonary arterial hypertension and systemic hypotension following rapid administration of hypertonic solutions has been described many times.[7-11]

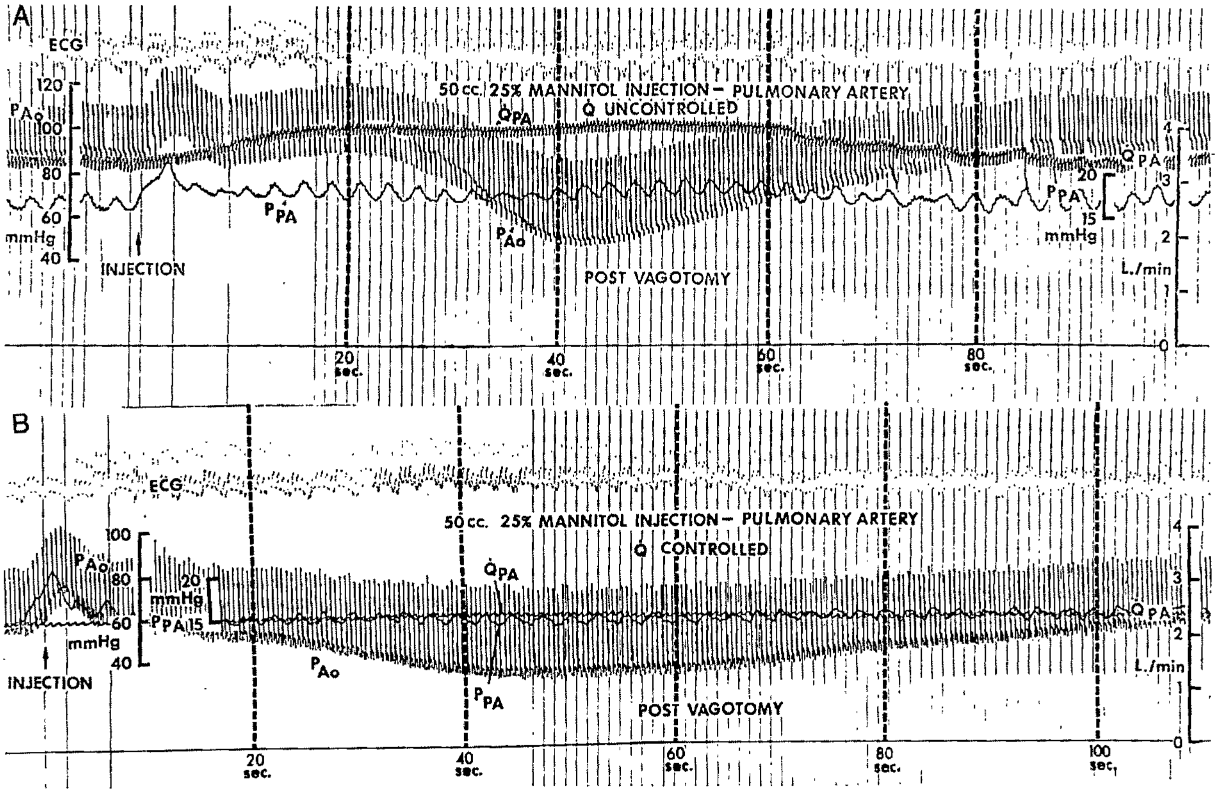

FIG 4. Traces as before, recorded after bilateral vagotomy. Hypotensive response is still present both when cardiac output is allowed to increase (A) and when cardiac output is controlled (B).

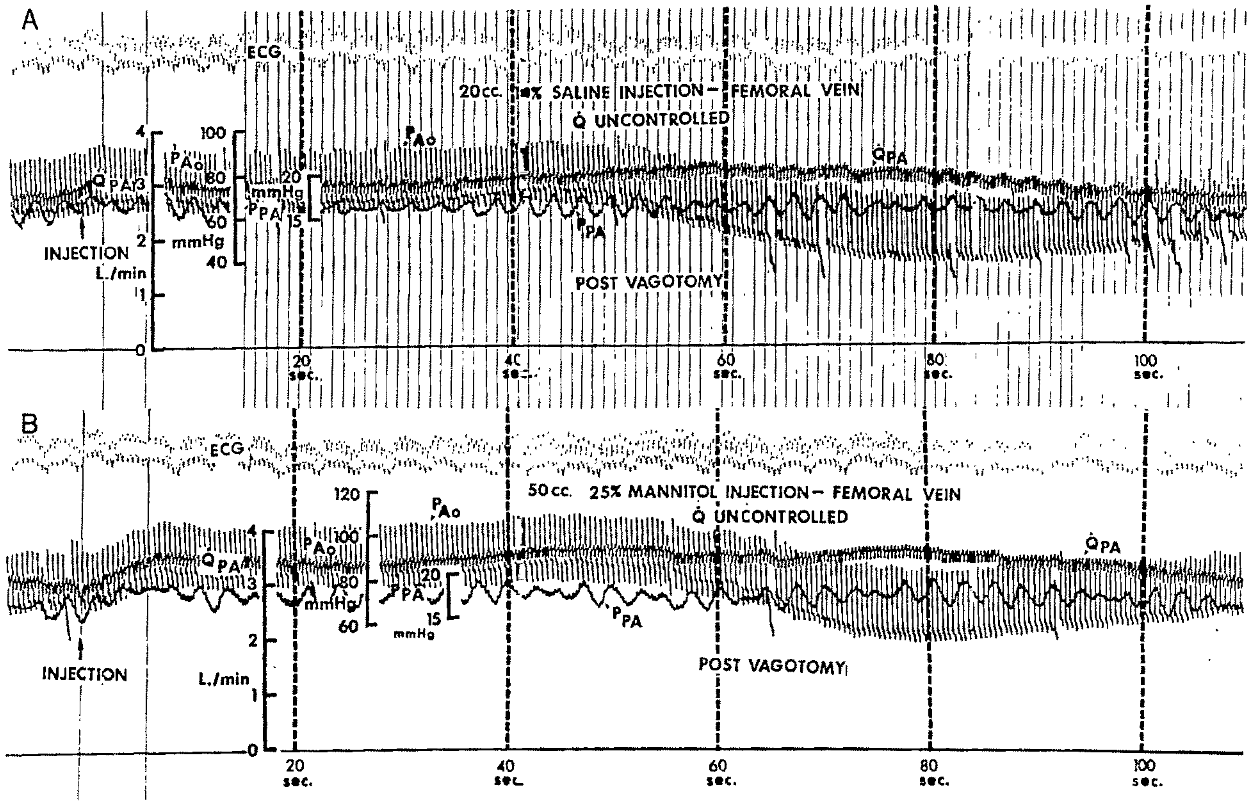

FIG 5. Femoral vein injection. Hypotensive response is delayed and injection artifact has been eliminated because of interposed right heart bypass system.

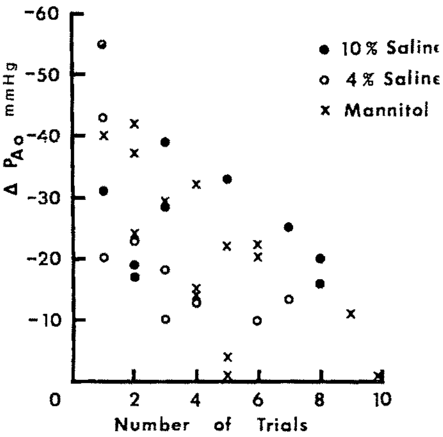

FIG 6. Decrease in aortic mean pressure in millimeters of mercury for all hyperosmolar injections including all three solutions (25% mannitol, 4% saline, and 10% saline) is plotted against the number of trials for all experiments. Total amount of osmotically active particles injected was kept constant for all injections. Response decreases with increasing number of injections. Data are both pre- and postvagotomy and following both pulmonary arterial as well as femoral venous injections.

The pulmonary circulatory changes have been observed only for the more extremely hypertonic NaCl solutions, and we find that mannitol does not fall into this category. Agarwald et al[7] noted that 20 ml of 3.6% or 7.2% NaCl did not produce a pulmonary hypertensive response.

Systemic hypotension in our experimental animals was seen with the lower as well as the higher osmolar solutions, and was seen following injection into either the pulmonary artery or the femoral vein.

Immediate onset of pulmonary edema is a very unlikely cause of respiratory distress following mannitol administration as we could demonstrate no changes in pulmonary arterial pressures or left atrial pressures. However, the consistent systemic hypotension, even in the face of increasing cardiac output caused by rapid injection of each of the three hypertonic solutions, suggests that the hyperosmolar challenge leads to release of a chemical mediator capable of inducing systemic vasodilation and, in the case of 10% saline, also pulmonary vasoconstriction. Failure of the hypotensive response after several injections could then indicate depletion of the mediator. If the hypotensive response to hyperosmolar solutions is caused by a mediator, that same mediator may, in some instances, cause bronchoconstriction. In clinical situations the rate of infusion of the hyperosmolar solution may be so slow or the several minutes of hypotension may not be noticed, but the response of an atopic individual could be exaggerated.

If the hypotensive response were due to release of mediators, it should be possible to show release phenomenon on exposure to hypertonic solution, and Lichtenstein and colleagues (Personal communication, 1978) did show that in our patient's blood small increases in osmolarity caused considerable histamine release from basophils. Whether histamine or some other mediator is responsible for the hypotensive response, some patients may be more sensitive to a mediator than others and may respond with profound hypotension and bronchospasm on a nonimmunologic basis.

In conclusion, the danger in the administration of mannitol may not always be solely that of fluid overload leading to heart failure and pulmonary edema. However, care should be taken when patients with minimal renal function receive very large doses of mannitol. If respiratory distress or hypotension occurs upon infusion of mannitol, it should not be misinterpreted as pulmonary edema and the treatment should be directed toward relief of bronchospasm and systemic vasodilation. The patient at risk is most probably an individual with a history of asthma.

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Adverse Effects of Sympatholytic Agents

Symptomatic sinus bradycardia developed in eight hypertensive patients treated with various sympatholytic agents: alpha-methyldopa in three patients; propranolol in two; clonidine in two; and guanethidine in one. On admission, in addition to sinus bradycardia (38 ± 5 beats/min) (mean ± SD), neurologic symptoms or hypotension, or both, were present in all. After cessation of drug therapy, heart rate increased to 60 ± 7 beats/min and symptoms disappeared. During a mean follow-up time of 15 ± 3 months, six patients were managed successfully by appropriate manipulation of their medical regimen, and two required permanent ventricular pacing. Electrophysiologic studies were performed in four patients, three of whom were challenged with intravenously administered propranolol (0.1 mg/kg of body weight). Abnormal responses to rapid atrial pacing occurred in all four patients. Increases in mean spontaneous cycle length and maximal sinus node recovery time occurred after propranolol administration. Severe bradyarrhythmias may be precipitated by sympatholytic agents, particularly in patients with sinus node disease. These bradyarrhythmias can usually be managed successfully by modification of the pharmacologic regimen. (*Scheinman MM, Strauss HC, Evans GT: Adverse effects of sympatholytic agents in patients with hypertension and sinus node dysfunction. Am J Med 64:1013–1020, 1978)*

CLINICAL reports

Wheezing After Induction of General Anesthesia: Negative Expiratory Pressure Revisited

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Wheezing is a high pitched musical sound caused by high velocity turbulent air flow in partially obstructed airways. The partial obstruction is usually due to active bronchoconstriction, either neurally or humorally mediated,[1] or to passive obstruction from a tumor or foreign body. The following case report describes wheezing due to passive airway collapse subsequent to inadvertent application of negative pressure during exhalation.

Case Report

An 81-year-old male was scheduled for a posterior fossa craniotomy for trigeminal neuralgia. Preoperative medical evaluation disclosed a 100-pack year smoking history and a 20-year history of multiple sclerosis. On physical examination significant findings were limited to the chest where an enlarged AP diameter and an increased expiratory phase, without wheezing, were noted. The electrocardiogram and laboratory values were within normal limits.

The patient was premedicated 90 minutes before the operation with diazepam, 10 mg orally, and atropine sulfate, 0.4 mg IM. On arrival in the operating room, electrocardiogram leads, a left radial arterial catheter, a right antecubital central venous pressure catheter, and a peripheral venous line were placed. Anesthesia was induced with droperidol, 5 mg IV, followed after 10 minutes by fentanyl, 0.2 mg IV, in four divided doses, and then sodium thiopental, 225 mg IV, in three divided doses. Relaxation was provided with pancuronium bromide, 8 mg IV. After endotracheal intubation and auscultation of the chest, the patient was positioned in the semi-sitting position. Continuous mechanical ventilation with nitrous oxide, 3 L/min, and oxygen, 2 L/min, was then begun, using an Ohio Fluidic Ventilator set to deliver a tidal volume of 1000 ml at a rate of eight times per minute. Following this, reauscultation of the chest revealed bilateral expiratory wheezing and a marked prolongation of expiration without a change in vital signs. Examination of the endotracheal tube for position and cuff inflation failed to reveal a cause of wheezing. Halothane 1.0% in the inspired gas had no effect on the wheezing and was discontinued when the patient developed isorhythmic dissociation with a decrease in blood pressure. Coincidentally, the airway pressure was noted to be −8 cm H_2O during expiration. A decrease of the expiratory flow rate eliminated this negative pressure and simultaneously eliminated the wheezing. After a 10-minute delay, a return to the initial airway pressure pattern reproduced wheezing whenever a negative expiratory pressure greater than −6 cm H_2O was introduced. The ventilator was then adjusted to eliminate negative pressure expiration, and the remainder of the case was conducted without further wheezing.

Discussion

The cause of wheezing in this patient was determined by a process of elimination. Passive airway obstruction from a tumor or foreign body seemed unlikely in view of a clear preoperative chest x-ray and an uneventful induction of anesthesia. Active bronchoconstriction then seemed most probable as the mechanism, mediated by either neural or humoral factors. The lack of variation in blood pressure and heart rate made a humoral factor, such as release of serotonin from a secreting tumor or release of histamine in response to an injected drug, improbable. It was therefore then assumed that the most likely diagnosis was neurally mediated bronchospasm, stimulated by endotracheal intubation of a lightly anesthetized and by history a highly reactive, airway. If this diagnosis were correct, introduction of halothane into the inspired gas should have served both as a means of increasing the depth of anesthesia and of directly decreasing bronchomotor tone.[1] Halothane, however, had no effect on the wheezing.

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Over a decade ago it was recognized that negative pressures as low as -3 cm H_2O when applied during exhalation could induce airway collapse, partial obstruction, and wheezing.[2] Modern anesthesia practice does not often make use of negative pressure ventilation and therefore its effect on airway resistance was not initially considered in the differential diagnosis of this patient's wheezing. At the onset of wheezing, immediate observation of the airway pressure through one entire respiratory cycle would have contributed to an earlier diagnosis of passive airway collapse with wheezing due to negative expiratory pressure.

The Ohio Fluidic Ventilator used in this case is designed with a bellows suspended from the top of a sealed chamber. During inspiration the bellows travels upward, driven by inflow of gas to the chamber, forcing gas into the anesthesia circle at a rate controlled by adjustment of inflow of gas into the sealed chamber. Expiration begins when gas stops flowing into the chamber; the bellows, driven by a large weight built into its base, then descends to baseline and in so doing aspirates gas from the anesthesia circle. The rate of descent of the bellows is controlled by adjustment of expiratory flow rate. The range of expiratory flow adjustment is great enough and the weight of the bellows heavy enough to allow the bellows to fall rapidly and to generate a negative pressure within the anesthesia circuit. During operation of this ventilator the magnitude of negative pressure generated during expiration is a function of the rate at which the bellows aspirates gas from the anesthesia circle system which, in turn, is a function of expiratory flow rate and the rate of fresh gas inflow into the anesthesia circuit. Patient expiratory flow rate is a function of airway resistance and the elastance of the lung. The greatest static negative pressure obtainable in the anesthesia circuit would therefore be during complete occlusion of the "Y" piece (simulating zero gas flow from the patient) and zero gas flow from the anesthesia machine. The manual supplied with the ventilator states that this maximum negative pressure capability is -9.5 cm H_2O. It is interesting to speculate that our emphysematous patient, who likely had increased airway resistance and decreased pulmonary elastance, would be most likely to experience wheezing when exposed to negative pressure during expiration. In addition, an emphysematous patient would have decreased airway structural rigidity and be most likely to narrow airways under negative pressure conditions and consequently wheeze.

In summary, the case illustrates two significant points. First, the Ohio Fluidic Ventilator can develop a negative pressure expiration which can be eliminated by decreasing expiratory flow rate. Second, negative pressure during expiration may cause wheezing during anesthesia.

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Periodic Apnea during Adenotonsillectomy

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Acute apnea induced with drugs and hyperventilation is a common anesthetic occurrence. Less common but of great interest is periodic apnea secondary to underlying pathology and not directly caused by an anesthetic. Periodic apnea is seen in patients with Pickwickian syndrome[1,2] and in some patients with chronic upper airway obstruction[3] secondary to a variety of causes.

The following case report demonstrates the need for a careful history in patients having tonsillectomy and adenoidectomy and shows that periodic sleep apnea associated with upper airway obstruction can persist even in the operating room and recovery room after the obstruction has been eliminated by an endotracheal tube.

Case Report

This was the first hospital admission of a 3½-year-old white

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male with the chief complaint of labored breathing and choking while asleep. Aside from a history of recurrent otitis media, the child had been in apparent good health. Tonsillar hypertrophy had been noted during physical examination 1 year prior to admission. Five days prior to admission the child experienced breathing difficulty with occasional apneic periods while sleeping. No apneic periods were noted while the patient was awake. The patient was scheduled for tonsillectomy and adenoidectomy with bilateral myringotomies and insertion of middle ear ventilating tubes Further history was unremarkable except for progressive difficulty swallowing during the 2 to 3 weeks prior to admission Physical examination revealed a well developed, well nourished white male child in no acute distress. Blood pressure was 100/64 mm Hg, pulse rate 136/min, respiratory rate 20/min, temperature 37.8 C, height 102.8 cm, and weight 15.5 kg. Examination of the head and neck revealed enlarged tonsils meeting in the midline, bilateral serous otitis media, micrognathia, and enlarged cervical lymph nodes.

The patient was seen in consultation and no evidence of cor pulmonale was found. Hemoglobin 12.2 gm/100 ml, hematocrit 35.5%, white blood count 8900; urine had a specific gravity of 1021 and was negative for protein, sugar, and acetone. Before premedication on the morning of the day of surgery the patient was quite somnolent and could barely be aroused from sleep. The semi-Fowler's position partially relieved his respiratory obstruction, but even in this position substernal retraction with cyanosis and periodic coughing episodes were observed. Premedication consisted of atropine, 0.2 mg IM, 90 minutes prior to surgery. He was placed in the supine position on the operating room table and tolerated this position without developing respiratory difficulties. Induction of anesthesia with halothane, nitrous oxide, and oxygen administered via a semiclosed system was uneventful. Endotracheal intubation with a 5.0-mm uncuffed orotracheal tube was easily accomplished without a relaxant. Anesthesia was maintained with halothane 1.5% and nitrous oxide-oxygen (4L:2L). Ventilation was spontaneous with occasional assistance. At no time did the patient receive narcotics, barbiturates, or muscle relaxants.

Approximately 30 minutes after induction of anesthesia, the patient developed periods of apnea lasting approximately 20 seconds preceded by three to five uniform breaths of apparently normal tidal volumes. No other changes in vital signs were noted during these periods of apnea. At 1½ hours after induction of anesthesia, the patient was taken to the recovery room with the endotracheal tube in place.

The apneic periods continued for another 40 minutes in the recovery room, during which time the patient was manually ventilated as needed. At the end of the period, the patient, fully awake and responsive, was extubated. No further apnea was noted and a 4-week follow-up revealed no further respiratory difficulties.

Discussion

In 1965 Noonan[4] and Menashe and associates[5] first reported that alveolar hypoventilation and cor pulmonale could result from hypertrophied adenoids and tonsils. The history of these patients as described by Djalilian et al[6] was one of "progression from frequent upper respiratory tract infections, mouth breathing and noisy nocturnal respiration to daytime lethargy, somnolence, and pulmonary hypertension." The parallel to the Pickwickian syndrome is striking and, in fact, in 1975 Sussman et al[2] reported two obese adults with periodic apnea, daytime somnolence, and hypertrophic tonsils in whom the periodic apnea and daytime somnolence were markedly improved after tonsillectomy.

In our patient, a pattern of periodic apnea was observed (under anesthesia and in the recovery period) characteristic of the Pickwickian syndrome. If this pattern were due solely to upper airway obstruction, one would expect it would disappear when the obstruction was eliminated by an endotracheal tube. Instead, it persisted, albeit transiently, during anesthesia and the recovery period. This is consistent with the findings of Coccagna et al,[7] who studied sleep polygraphs (electroencephalography and spirometry) following tracheostomy in three patients with hypersomnia and periodic breathing secondary to upper airway obstruction. Although the diurnal somnolence disappeared in all patients, periodic nocturnal apnea persisted to some degree for a variable period following relief of airway obstruction. Similarly, Sackner and associates[3] described a patient treated successfully with methylphenidate hydrochloride (Ritalin) when periodic apnea with cyanosis persisted for 2 days following tracheostomy for hypersomnia with airway obstruction.

Tassinari et al[8] divide periodic apnea into three types, based on electromyography and spirometric criteria. These are:

1. Central apnea, characterized by "complete absence of thoracic movements and of respiratory airflow."
2. Obstructive apnea "during which there is absence of respiratory airflow despite the persistence of a central respiratory drive as shown by diaphragmatic contractions and related chest movements."
3. Complex apnea characterized by "a short period of central apnea followed by a prolonged obstructive apnea."

In the first group (pure central apnea) are included a small number of patients with insomnia and narcolepsy described by Guilleminault et al,[9] and patients who continue to have apneic episodes after tracheostomy or endotracheal tube insertion have relieved their obstruction. All other patients have either purely obstructive apneas, complex apnea, or a combination of all three forms. These include patients with Pickwickian syndrome[2] and upper airway obstruction secondary to a variety of causes such as adenotonsillar hypertrophy,[4, 10] micrognathia,[2, 3] trauma to the temporomandibular joint,[11] or laryngeal stenosis.[7]

The pathophysiology of obstructive apnea is at present imperfectly understood. The daytime hypersomnolence that occurs is believed to result from the arousal and sleeplessness that follows each apneic period. Sackner et al[3] reported that these patients hardly ever reach the depth of sleep that normal subjects attain. Their sleep apnea occurred every 1.75 minutes and lasted between 20 to 40 seconds. Mangat et al[12] reported periods of apnea lasting as long as 108 seconds. The fact that these periods of apnea occurred only during sleep demonstrates the role of conscious voluntary effort in maintaining normal alveolar ventilation. Hypercarbia, so important in the etiology of respiratory depression in chronic obstructive lung disease, is not as prominent with periodic sleep apnea.[5] The patient falls asleep with a normal or only slightly elevated Pa_{CO_2}. While he sleeps, there is a marked reduction in oropharyngeal and intercostal tone as substantiated by electromyographic and cinefluoroscopic recording[13]. He cannot overcome his obstruction and although he may make respiratory efforts, he becomes effectively apneic. Pa_{CO_2} rises and Pa_{O_2} falls. He partially awakens and resumes breathing. This pattern of apnea-arousal-ventilation may occur approximately once every 2 minutes throughout the night. The patient can be thought of as conditioning himself to the apnea so that even with removal of obstruction the pattern persists. The cases of Coccagna et al[7] and Sackner et al[3] as well as our case fit this picture and underline the necessity of careful postoperative monitoring following adenotonsillectomy. We feel that more diligent observation will reveal that periodic apnea during anesthesia and in the recovery period is not uncommon.

The condition is indeed a reality but appears to be of limited duration. Awareness of this syndrome is of greater importance than any fear it might engender. Patience along with constant observation is the treatment. If apneic episodes are noted, with or without changes in vital signs, ventilation should be gently assisted, if necessary, until a normal respiratory pattern is observed.

In summary, we describe a patient with the obstructive syndrome who developed periodic apnea after endotracheal intubation. We feel that periodic central apnea under anesthesia is more common than previously appreciated and necessitates careful postoperative and intraoperative monitoring of respiration in the obese or chronically obstructed patient.

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Apnea with Maintenance of Consciousness, following Intravenous Diazepam

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Apnea following intravenous diazepam has been reported previously,[1, 2] but not in a patient who has had recall of the apnea.

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A healthy A.S.A. class I 69-year-old woman was taken to the operating room for open reduction and internal fixation of the right hip. She was not premedicated and had been taking no medicines. Upon arrival in the operating room, she was given 5% dextrose in lactated Ringer's solution intravenously. Blood pressure was 140/90 mm Hg with a pulse rate of 90/minute. The electrocardiogram showed a normal sinus rhythm. The patient was alert and cooperative, but complained that she was nervous.

The patient was given 2.5 mg of IV diazepam without being told that she was receiving anything. Almost immediately she began to move her extremities in a random manner. The movements did not resemble those associated with succinylcholine, and there is no chance that succinylcholine could have been given inadvertently. She was asked what was wrong, but did not answer. It was then noted that she was apneic and controlled ventilation was begun by mask with 100% O_2. Body movements had ceased by this time.

After 2 to 3 minutes, the patient began breathing spontaneously and within another minute she opened her eyes and pulled the mask to her face, saying that she needed oxygen. Her pulse rate was 120 beats/minute with a blood pressure of 155/110 mm Hg. She was diaphoretic and very nervous. The ECG was unchanged except for a sinus tachycardia. She complained that she had not been able to breathe or talk.

Anesthesia was then induced with 200 mg of thiopental. Endotracheal intubation was facilitated with the use of succinylcholine. Anesthesia was maintained with 0.5% enflurane, 60% nitrous oxide in oxygen, and 15 mg of morphine. Recovery was rapid and uneventful. The patient was very relieved that the operation was over and that she was alive. She said that prior to induction of anesthesia she had moved her extremities about to call to someone's attention the fact that she could not breathe or talk. She remembered being asked what was wrong and thinking that she was going to die. After that she had no recall until spontaneous ventilation resumed in 2 to 3 minutes.

Discussion

Larson and associates[2] reported a case of apnea following 2.5 mg of diazepam in a healthy patient who was not premedicated. However, their patient had no recall of the apnea. The apnea and unconsciousness were reversed in 1 to 2 minutes with physostigmine. The patient presented here was conscious for at least the early part of her apnea and the experience was quite disturbing to her. Her apnea resolved spontaneously in 2 to 3 minutes.

Anyone administering intravenous diazepam to any patient should be capable of giving controlled ventilation. In patients with a full stomach, the ability to intubate would be advisable. Physostigmine should be available in the event that reversal of the effects of diazepam is needed.

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An Inexpensive Portable Positive End-Expiratory Pressure System

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Positive pressure ventilation has become the cornerstone of therapy for respiratory distress patients of all ages. Those with aspiration pneumonitis surfactant deficiencies, and a variety of other processes may also require addition of positive end-expiratory pressure (PEEP) to achieve adequate arterial blood gases.[1,2] PEEP opposes alveolar collapse that may occur in portions of lung that have marginal ventilation perfusion ($\dot{V}_a/\dot{Q}$) characteristics. Abrupt discontinuation of PEEP can cause equally rapid respiratory decompensation due to hypoxemia. Patients in respiratory failure who require PEEP may require transportation for therapy or diagnostic studies.[3] Maintenance of PEEP has proven a cumbersome task when these patients are moved. Despite these difficulties, transfer within or between hospitals is not a justifiable

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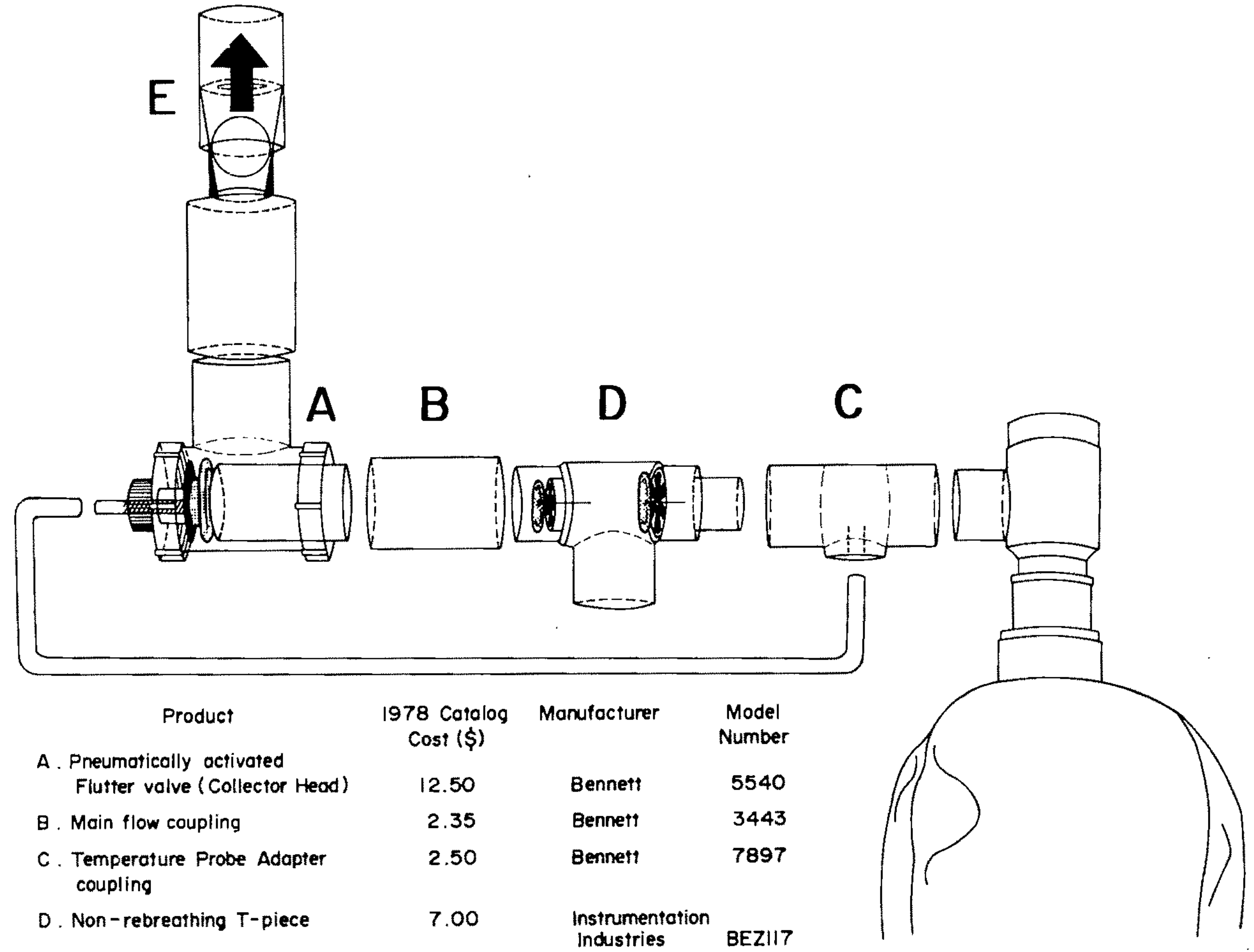

Product	1978 Catalog Cost ($)	Manufacturer	Model Number
A. Pneumatically activated Flutter valve (Collector Head)	12.50	Bennett	5540
B. Main flow coupling	2.35	Bennett	3443
C. Temperature Probe Adapter coupling	2.50	Bennett	7897
D. Non-rebreathing T-piece	7.00	Instrumentation Industries	BEZ117
E. PEEP valve	46.00–84.00 (Kit price varies)	Boehringer	4800 4802 4812

FIG 1. Exploded view of portable PEEP apparatus. Components were selected solely on a performance basis. Similar parts from other manufacturers may be substituted without changing the characteristics of the system.

reason to discontinue PEEP therapy in critically ill patients. We have developed a portable PEEP maintenance system that can be readily assembled from components found in most respiratory therapy units. It is essentially a modified Mapelson A non-rebreathing circuit. Components are a pneumatically activated flutter valve (collector head), assorted couplings, a unidirectional T-piece, and a dead weight PEEP valve (Fig 1). A resuscitation bag serves as a reservoir for manual ventilation and provides a safety inflow valve. Only bags adapted to deliver 100% oxygen should be used since inspired oxygen concentration (F_{IO_2}) may vary with fresh gas inflow rates in unmodified bags.[4, 5] It is important to rememeber that circuits utilizing non-rebreathing valves require gas inflow rates that meet or exceed estimated minute ventilation to prevent rebreathing. A piece of delivery tubing, as found in various disposable oxygen enrichment kits, is the pneumatic connection between the collector head (A) and the temperature probe adapter coupling (C) orifice. When the resuscitation bag is compressed, the pneumatic valve in the collector head occludes the expiratory limb of the circuit and permits inhalation from the fresh gas source. During exhalation, the pneumatic valve opens and the one-way T-piece routes expired gases through the PEEP valve (E). Close examination of Fig 1 reveals that the second unidirectional valve (distal to the bag) within the T-piece (D) is redundant. Removal is simple but has proven to be unnecessary.

The PEEP valves are ideally suited for portable use. Moisture does not affect their function because they operate on a dead weight principle.[6] They are not flow dependent and can be changed quickly. Accurate

Patient	Event Precipitating Respiratory Distress	Age	P_aO_2 (Torr)* Bedside	P_aO_2 (Torr)* Transport
1	Pancreatitis	56	88	84
2	Post thoractomy	69	166	153
3	Pulmomary edema after head trauma	18	119	108
4	Abdominal aortic aneurysm resection	71	210	196
5	Aspiration pneumonitis	25	134	150
6	Chest trauma & multisystems injuries	48	76	68
7	Fulminant sepsis	19	90	85
8	Aspiration pneumonitis	32	138	138
9	Ileal bypass for obesity	31	104	98
10	Hepatic abcess and renal failure	46	67	69
Mean±SD		37.6±19.8	118.2±41.4	115.0±42.6†

FIG 2. Arterial oxygen partial pressures of patients at bedside and during transportation. Patients were randomly selected. Selection criteria were respiratory distress requiring (1) mechanical ventilation, (2) inspired oxygen concentration of 100%, and (3) positive and expiratory pressure of 5 cm or more of water to maintain acceptable arterial oxygen partial pressures.* $F_IO_2 = 1$ at flow rates of 5 to 7 L/min.† No significant difference from bedside values ($p > 0.05$), Student's *t*-test.

calibration is assured if the valves are kept within 10 degrees of vertical. Addition of a lightweight electronic spirometer permits measurement of tidal volume and minute ventilation. For patients in whom airway pressure is critical, an anaeroid manometer can be coupled to a single arm manifold on either side of the T-piece.

The system has been used without incident in 10 randomly selected patients requiring PEEP levels ranging from 5 to 15 cm H_2O. Arterial blood samples for Pa_{O_2} determination were obtained while patients were stable on ventilators prior to being transported. The portable PEEP system (with two oxygen E cylinders for the gas source) was then applied. Arterial blood samples were later obtained to determine Pa_{O_2} when the system was in use during transportation (Fig 2). These paired data were analyzed for statistical significance of their differences using Student's *t*-test. No significant differences were found ($p > 0.05$).

The system for portable PEEP presented here fulfills the ideal criteria for this type of device, i.e., safe, inexpensive, adaptable, lightweight, and easy to assemble.

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Ischemic Injury following Uncomplicated Radial Artery Catheterization

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Arterial occlusion by local thrombus formation or embolization is a serious complication of radial artery catheterization. The literature is replete with reports of ischemic injury as a result of radial artery cannulation in patients with impaired perfusion or an unstable perioperative course.[1-4] This report documents the occurrence of permanent ischemic injury requiring digital amputation. To our knowledge this is the first report of this occurrence in a patient who had a normal preoperative Allen's test and an uncomplicated hospital course.

Report of a Case

A 54-year-old man was admitted to the hospital for coronary artery bypass surgery. Fourteen years prior to admission he had bilateral iliac thromboendarterectomies for claudication; there was no recurrence of signs or symptoms. Three years prior to admission he had an uncomplicated inferior wall myocardial infarction; there was no history of angina. One month prior to admission he had a

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cardiac arrest without evidence of a myocardial infarction. He had a 40-pack/year history of cigarette smoking without evidence of pulmonary disease.

Physical examination, including bilateral Allen's tests, was normal. Routine laboratory tests, coagulation studies, chest roentgenogram, and pulmonary function tests were within normal limits. The electrocardiogram revealed an old inferior wall myocardial infarction without acute changes. Cardiac catheterization prior to admission was conducted via the right brachial artery and revealed inferior wall dyskinesis with an ejection fraction of 52%, a left ventricular end-diastolic pressure of 8 torr, 95% occlusion of the right coronary artery, and 80% occlusion of the left anterior descending artery.

Prior to induction of anesthesia, a right peripheral intravenous catheter was placed, and a pulmonary arterial catheter was inserted via the right internal jugular vein. A #20 Long Dwel catheter (Becton, Dickinson & Company, Rutherford, New Jersey) was placed percutaneously in the left radial artery on first attempt without difficulty. A continuous infusion of heparinized 0.9% normal saline (2 units/ml) was maintained at a rate of 3 ml per hour with an Intraflow system (Sorenson Research, Salt Lake City, Utah).

The left arm was extended at the shoulder and flexed at the elbow without tension on the brachial plexus. It remained under direct observation throughout surgery. There was no evidence of compromised perfusion. Anesthesia consisted of morphine sulfate (100 mg), diazepam (20 mg IV), and 60% nitrous oxide. Pancuronium was used for paralysis, and ventilation was controlled. Anesthesia and surgery proceeded without incident and the right, left anterior-descending, and obtuse-marginal coronary arteries were bypassed; extracorporeal perfusion time was 2 hours, including 58 minutes during which the aorta was cross-clamped. Mean radial arterial blood pressure ranged from 60-80 torr during cardiopulmonary bypass and pressures ranged from 100/60 to 140/80 torr in the post-bypass period. No vasopressors were used either intraoperatively or postoperatively. Esophageal temperature ranged from 32-37 C.

Postoperatively the patient did well and was hemodynamically stable with good peripheral perfusion. His endotracheal tube was removed 12 hours postoperatively without complications.

Thirty-six hours after cannulation of the radial artery the patient complained of left forearm pain and stated that he had experienced mild pain intermittently over the prior 12 hours. The arterial line functioned well, and there was no evidence of vascular compromise. However, the arterial line was discontinued because of the symptoms. Examination after decannulation revealed absence of the left radial artery pulse; the left ulnar pulse remained full. No skin, color, or perfusion changes were noted.

Forty-two hours after cannulation (6 hours after decannulation), discoloration was noted over the volar surface of the left hand extending from the thenar eminence to the distal segments of the thumb and index finger. Over the next 6 hours, the patient experienced hyperesthesia accompanied by progressive mottling over this distribution. The left radial pulse remained absent; the ulnar pulse remained full. There was no evidence of infection. The third, fourth, and fifth fingers remained normal.

In an attempt to augment perfusion of the left forearm and hand, a left brachial plexus block via the axillary approach was performed without arterial penetration. Forty milliliters of 0.5% bupivicaine without epinephrine was instilled. Complete sensory and motor blockade resulted, but there was only a small transient improvement in perfusion. Anticoagulation with heparin, 5000 units IV every 6 hours, was initiated.

Because of the persistent mottling, temperature difference, and absence of pulsation, the left radial artery was surgically explored. At operation the findings included one site of arterial puncture with proximal thrombus formation, and poor back-bleeding; there was no hematoma. A thrombectomy was performed and produced return of the radial pulse. In addition, brachial plexus block was repeated three times over the following 48 hours. Despite this, the mottling progressed over the next 4 days. The ischemic area was defined by the volar distribution of the left radial artery. Amputation of the involved areas was performed several weeks later.

Discussion

Despite the relatively high reported incidence of transient thrombosis (up to 88%),[5,6] occlusion post-decannulation (up to 60%),[4] and hematoma formation (up to 50%),[6] permanent ischemic injury secondary to percutaneous radial artery cannulation has been rarely reported, and then only in association with other complicating factors. These factors include previous arterial injury,[7] hypotension,[8] use of vasoactive agents,[8] prolonged cannulation[9] left heart embolization,[8] and infection.[10]

Presented here is a patient who, in spite of a normal preoperative Allen's test and an uncomplicated perioperative course, suffered a rapidly progressive ischemic injury resulting in amputation of the distal segments of two fingers. Noteworthy is the fact that the only presenting symptom was intermittent forearm pain beginning 24 hours after cannulation without associated signs of decreased perfusion until 6 hours after decannulation when rapidly progressive signs of ischemia occurred. We believe that this injury probably resulted from emboli which arose from the site of radial arterial puncture and which, after passing peripherally, involved the distal arteries of the index finger and thumb. Poor back-bleeding in the face of a normal preoperative Allen's test and full ulnar pulse suggest involvement of the palmer arch as well.

We suggest that decannulation should be done as soon as clinically appropriate[11] or whenever any symptoms suggestive of impaired perfusion develop. The efficacy of other forms of therapy such as repeated sympathetic blockades, systemic anticoagulation, and thrombectomy cannot be assessed.[4]

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Apparent Resistance to Succinylcholine

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The following is a clinical report of apparent resistance to succinylcholine in a patient undergoing electric shock treatments. Our methods for the anesthetic management of patients having electric shock treatments were gradually developed during several years of interdepartmental consultations and experience. Patients receive 0.2 to 0.4 mg of atropine 1 hour prior to treatment; next the patients are given a 50-mg test dose of thiopental which is followed by additional thiopental, the amount depending upon response to the test dose, plus succinylcholine as a single injection. Manual positive pressure ventilation is then instituted until anesthesia with relaxation occurs, the electric shock then being administered by the psychiatrist after insertion of a U-shaped bite block. Further manual ventilation is continued until clinically adequate breathing returns, usually in 2 to 4 minutes. Amounts of thiopental and succinylcholine administered, usually 300 to 400 mg and 40 mg, respectively, for the initial treatment, are adjusted during subsequent treatments to provide amnesia for the shock by the thiopental together with modification of somatic response to shock by succinylcholine to the extent that moderate muscular contraction occurs during application of electric current, followed by mild clonus of legs and forearms which gradually ceases within about 10 seconds after the current is stopped. Treatments are administered on alternate days, six to 12 treatments usually being given depending upon clinical response of the patient. All treatments are given in the recovery room where patients remain for observation until they can be safely returned to the ward.

Report of Case

A 52 year-old Caucasian man was admitted with a history of mental depression and hematemesis. He weighed 90 kg and his height was 156.2 cm. Delta-computed axial tomography and pneumoencephalography showed minimal cerebral atrophy. Medical evaluation and extensive laboratory studies were otherwise essentially normal and he was transferred to the psychiatric service for treatment of mental depression. He had initially received imipramine, 150 mg orally h.s., for 4 days. This was increased to 200 mg orally h.s., for 11 days before being discontinued as ineffective 3 days prior to institution of electric shock treatments.

He had no history of exposure to either anticholinesterase or cholinesterase reactivator drugs.

Anesthesia for the first electric shock treatment was in the usual manner. Atropine, 0.2 mg, was administered 1 hour prior to treatment. Thiopental, 50 mg IV, followed by 400 mg, produced clinical anesthesia, loss of eyelid reflexes, and respiratory depression. Succinylcholine, 40 mg, was given intravenously. Fasciculation did not occur, but was thought to be masked by the thiopental. Electric shock was associated with unusually intense somatic contraction followed by strong generalized clonus gradually ceasing over about 30 to 45 seconds after the current had been stopped.

The patient was given a second electric shock treatment 2 days later. Thiopental, 50 mg, followed by 300 mg, produced somnolence and loss of eyelid reflexes without clinically significant respiratory depression. Succinylcholine, 50 mg, was administered. There was no apparent response to the succinylcholine and an additional 40 mg were given after 3 minutes, again without apparent effect. The psychiatrist did not wish to abandon treatment and two additional doses of succinylcholine of 40 mg each were given using different vials at 2- to 3-minute intervals; neither of these produced visible fasciculation or relaxation. Electric shock was administered in the absence of apparent muscular relaxation, the anesthesiologist not wanting to give additional succinylcholine in these unusual circumstances. Somatic response, similar to that observed during the first treatment, was not satisfactorily modified.

Succinylcholine from each of the vials, which were apparently ineffective in this patient, produced the expected fasciculation and relaxation in 40-mg doses when subsequently given to other patients undergoing surgery.

A venous blood sample from the patient showed a plasma cholinesterase level of 3.0 delta pH units/hr (normal:0.41 to 1.65

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delta pH units/hr) and a dibucaine number of 87 (normal: about 80).

Two days after the second treatment the patient was given thiopental, 350 mg, and succinylcholine, 80 mg, for the third electric shock treatment. Weak fasciculation was seen only on the right side of the neck and paralysis was about 50% as clinically judged by respiratory depression. Modification of response to electric shock treatment was fair, somatic response being less than in the first two treatments, but stronger than our desired standard.

The patient had five additional treatments on alternate days with the same amount of thiopental (350 mg), but with 100 mg of succinylcholine being used each time. Weak fasciculation occurred around the eyes, on both sides of the neck, and in both feet; about 75% paralysis was achieved as judged clinically on the basis of respiratory depression. These treatments were satisfactory, the somatic response corresponding to our criteria each time.

Clinically normal breathing returned immediately after each electric shock treatment. Vital signs remained stable and emergence from anesthesia was rapid.

Another venous blood sample from the patient after completion of the electric shock treatments showed a plasma cholinesterase level of 2.74 delta pH units/hr and a dibucaine number of 87.

He was discharged improved.

Discussion

Pseudocholinesterase (serum cholinesterase) is the enzyme responsible for hydrolysis of succinylcholine to choline and succinylmonocholine. In the majority of patients with normal serum cholinesterase, succinylcholine is hydrolyzed rapidly as it circulates through the blood, only small fractions reaching the myoneural junction, its site of action.[1] The capacity to hydrolyze succinylcholine in human serum depends upon both type and concentration of serum cholinesterase, through there is no correlation between type and concentration of the enzyme.[2]

Typical and atypical forms of serum cholinesterase are established by measuring the degree to which dibucaine inhibits the hydrolysis of a suitable substrate by pseudocholinesterase, the results being expressed as the dibucaine number. Dibucaine numbers are divided into three groups on a genetic basis: those above 70, those between 45 and 70, and those below 25. Normal values (about 80) for dibucaine numbers, present in about 97% of the population, represent individuals who are homozygous for the normal, typical form of pseudocholinesterase. About 3% of the population are heterozygous for atypical forms of pseudocholinesterase, with dibucaine numbers between 45 and 70; these individuals metabolize succinylcholine about as rapidly as do individuals with normal dibucaine numbers. Dibucaine numbers below 25 are encountered in those rare individuals who are homozygous for atypical forms of pseudocholinesterase. These are the individuals who, unable to metabolize succinylcholine at normal rates, have prolonged responses to succinylcholine. It is not clear how atypical esterases, which account for the largest number of abnormal responses to succinylcholine, differ from normal esterase in its structure, but there are differences in catalytic activity.[1] Abnormally low dibucaine numbers, however, are associated with increased responses to succinylcholine or prolonged duration of action. Quite obviously our patient had neither of these reactions. On the contrary, he appeared to be resistant to succinylcholine. The fact that he had a normal dibucaine number indicates only that he was homozygous for the normal type of serum cholinesterase.

However, responses to succinylcholine are influenced not only by the type of pseudocholinesterase, but also by its level of activity. Factors other than genetically transmitted forms of atypical pseudocholinesterase may also cause variation in serum cholinesterase activity. Oximes, cholinesterase reactivators used in treatment of exposure to organophosphorus compounds, for example, increase activity and so may shorten the duration of action of succinylcholine or even prevent it from having appreciable effect. Edrophonium, pyridostigmine, physostigmine, neostigmine, benzpyrinium, demecarium, and ambenonium[3] as well as some bronchogenic tumors, malnutrition, motoneuron disease, myasthenia gravis, organophosphates, and some antibiotics,[4] on the other hand, have an inhibitory effect on serum cholinesterase and thus increase sensitivity to succinylcholine and prolong its effect.

The present case of apparent resistance to succinylcholine occurred in an institution in which detailed biochemical data regarding serum cholinesterase enzyme kinetics are not available. The clinical history, however, makes it unlikely that the apparent resistance was drug-induced. There was no history of exposure to known cholinesterase reactivators (oximes). Imipramine, commonly used as an antidepressant for mental depression, has not been reported as altering pseudocholinesterase activity. Furthermore, samples of succinylcholine from the same vials subsequently administered to other patients having surgery produced normal and expected responses. Serum cholinesterase type (dibucaine number) was normal. The patient may have been resistant to succinylcholine because of an increased amount or activity of pseudocholinesterase, as is suggested by the finding that the plasma cholinesterase level following the second electric shock was 3.0 delta pH units/hr, 5 SD above the mean. The normal range of 0.41–1.65 delta pH units/hr encompasses ± 2 SD from the mean for this laboratory; the level of 3.0 in this patient is clearly abnormal (Personal communication. Perna VP: Director, Smith Kline Clinical Laboratories Inc.). Two weeks later a second plasma cholinesterase level was still elevated, 2.74 delta pH units/hr, more than 4 SD above the mean. The second serum cholinesterase level verifies the original abnormal level and suggests that repeated succinylcholine administration had no significant effect on enzyme levels or activity.

In summary, a 52-year-old man undergoing thiopental-succinylcholine anesthesia for administration of electric shock treatments did not demonstrate clinical fasciculations and muscular relaxation from succinylcholine given in the doses we are accustomed to administering. He showed unusually strong somatic reaction to applied electric shock. Venous blood samples showed elevated serum cholinesterase levels of a normal type. Based upon this elevated serum cholinesterase level and observed clinical changes in patient response to electric shock treatment with increased amounts of succinylcholine, it is hypothesized that the elevated concentration of normal serum cholinesterase produced unusually rapid hydrolysis of the succinylcholine resulting in apparent resistance.

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Mainstem Bronchial Rupture during General Anesthesia

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Rupture of the trachea or bronchi can be one of the most serious complications of endotracheal intubation. In most instances it has been due to trauma or pathologic changes involving the major airways. This paper presents a case of rupture of the left mainstem bronchus in the absence of trauma or gross airway pathology.

Report of a Case

A 33-year-old white woman was admitted to the hospital for elective total abdominal hysterectomy for adenomyosis of the uterus. In 1973 the patient had a spinal anesthetic for tubal ligation which was complicated by what she described as "going into shock." She gave no history of cough, respiratory infection, bronchitis, asthma or emphysema. She smoked 15 cigarettes per day for 14 years.

The physical examination, laboratory data, and preoperative chest x-rays were normal (Fig 1). Premedication for general endotracheal anesthesia consisted of intramuscular morphine, 8 mg, and scopolamine, 0.4 mg. Monitors included an ECG and a blood pressure cuff.

Induction of anesthesia was accomplished with intravenous 2% thiopental, 400 mg, followed by ventilation with 100% O_2 by mask and 60 mg of succinylcholine. Direct laryngoscopy performed gently revealed a normal glottis which was sprayed with 4 ml of 4% lidocaine. The trachea was then atraumatically intubated with an 8-mm Argyle cuffed endotracheal tube without a stylet. The endotracheal tube was placed so that the cuff was just below the vocal cords. The intubation was not associated with bucking or coughing. Six milliliters of air provided an adequate seal between the trachea and endotracheal tube. Peak pressures during manual ventilation were low, never exceeding 25 cm H_2O.

Within the first 30 second of manual positive pressure-ventilation with N_2O-O_2, subcutaneous emphysema of the left side of the face and neck developed and the blood pressure fell slightly. Breath sounds at this time were normal and equal bilaterally. Nitrous oxide was discontinued. Despite minimal positive pressure used to maintain ventilation, peak pressures less than 20 cm H_2O, the subcutaneous emphysema progressed to involve the left shoulder, neck, and eyelid. Auscultation of the chest now revealed normal heart tones, crackling crepitus, and decreased breath sounds on the left side.

X-ray of the chest confirmed the clinical diagnoses of marked subcutaneous emphysema, pneumomediastinum, and left pneumothorax (Fig 2). This chest film also showed that the endotracheal tube was well placed in the trachea with the tip at least 5 cm above the carina. A thoracic surgeon immediately inserted a left chest tube. The chest tube and waterseal drainage system relieved the pneumothorax and halted the progression of the subcutaneous emphysema of the left neck and face. Fiberoptic bronchoscopy

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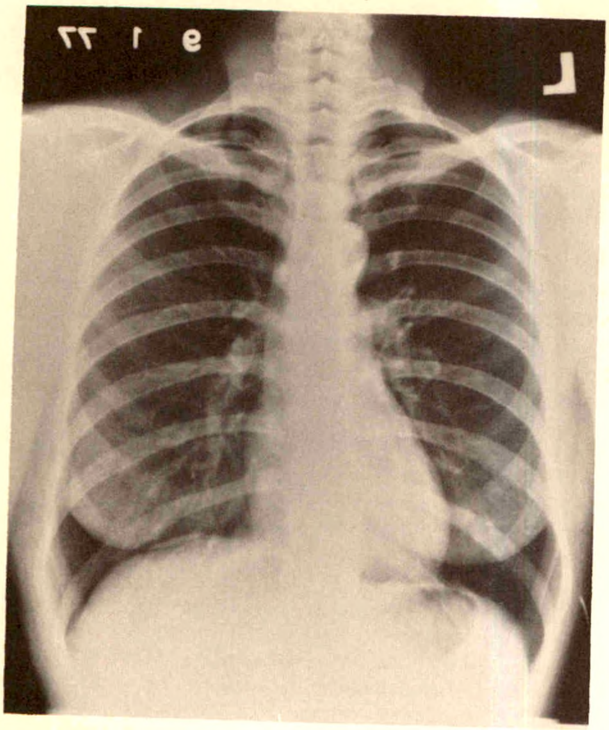

FIG 1. Normal preoperative upright PA chest film in 33-year-old white woman.

revealed a 2-cm rupture of the left mainstem bronchus extending into the carina and about 0.5 cm up the posterior wall of the trachea. The tracheobronchial tree appeared otherwise normal.

Surgery was postponed and conservative treatment of the bronchial rupture decided upon. The patient was extubated while anesthetized to prevent coughing. The endotracheal tube was examined carefully and had no rough edges or defects. A chest x-ray repeated 45 minutes after induction revealed a fully reexpanded left lung, normal right lung, pneumoperitoneum, pneumopericardium, and regression of the cervical subcutaneous emphysema (Fig 3).

In the intensive care unit the patient was awake and alert, her vital signs were stable, and she had no evidence of respiratory embarrassment. Because no air leak was observed during spontaneous ventilation, nonoperative management was continued and the bronchial rent apparently healed without further complication. The chest tube was removed on the 2nd postanesthetic day. On the 5th postanesthetic day the chest film was normal (Fig 4) and she was discharged from the hospital. She subsequently underwent uneventful total abdominal hysterectomy with spinal anesthesia.

Discussion

Case reports of perforation of the trachea or bronchi associated with instrumentation of the airway indicate that such a complication is usually related to preexisting pathology or malformation of the airway,[1] the use of stiff endotracheal tubes or sharp protuberant

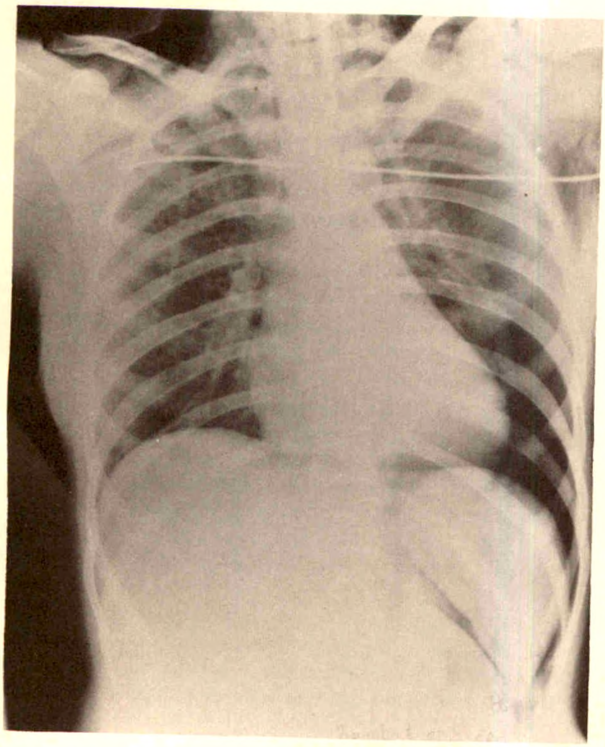

FIG 2. Recumbent AP chest film taken after induction of anesthesia showing marked subcutaneous emphysema, mediastinal, and peribronchial air dissection, and left pneumothorax.

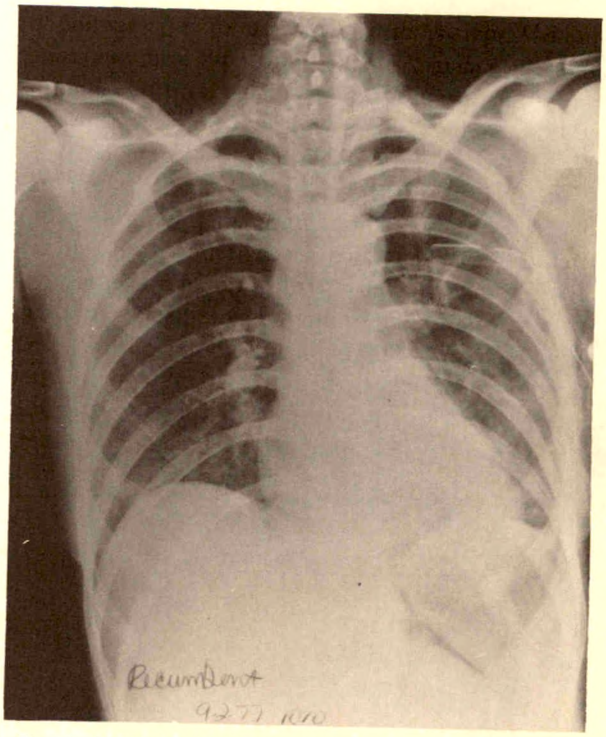

FIG 3. Recumbent AP chest film taken 45 minutes after induction of anesthesia after insertion of left chest tube. Note the reexpansion of the left lung, regression of the cervical subcutaneous emphysema, and presence of pneumoperitoneum and pneumopericardium.

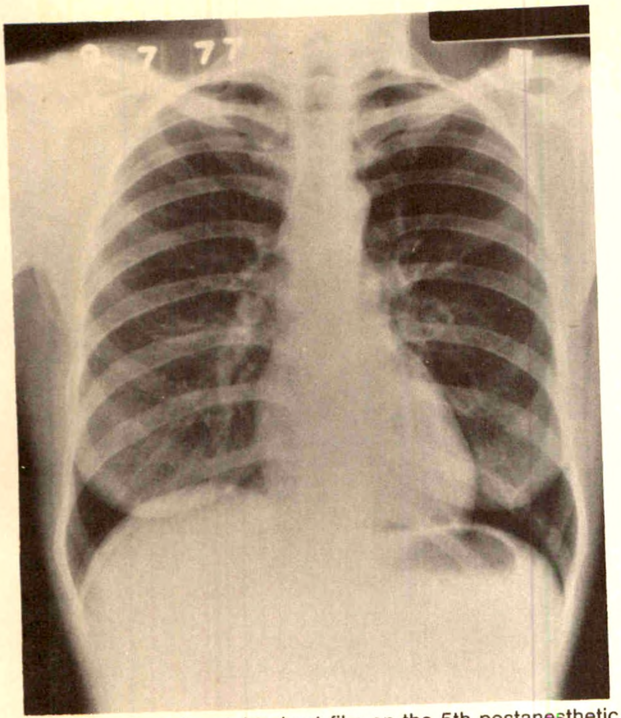

FIG 4. Normal upright chest film on the 5th postanesthetic day.

stylets, repeated or forceful attempts at intubation,[2] over-inflation of the endotracheal tube cuff,[3] hyperextension of the neck,[4] traction on the trachea during thoracotomy,[2] or bouts of coughing or violent movements of the head or neck. Elderly patients and infants[5] are reported to have fragile airways susceptible to spontaneous rupture. Our case had none of these features usually associated with tracheal rupture. Because manual ventilation pressures never exceeded 25 cm H_2O, it is unlikely that the positive-pressure ventilation actually caused the airway rupture. We can only guess that the rupture was preexistent from unknown causes and that the positive-pressure ventilation made the rupture evident.

Rupture of the trachea or bronchi usually occurs posteriorly, as in our case, because the posterior wall is membranous and unsupported by cartilagenous rings. When tracheal or bronchial rupture occurs, air enters the pretracheal fascial plane and dissects cephalad into the mediastinum and neck and/or caudad along the prevertebral fascial planes.[6] Clinical diagnosis of large airway rupture can be made by the immediate appearance of subcutaneous emphysema in the neck,[7] followed by pneumomediastinum causing cardiopulmonary embarrassment, and, later, pneumothorax, pneumoperitoneum, and even pneumopericardium. Open-chest surgical repair of large airway rupture is usually necessary if air leakage continues. Our case demonstrates that surgical repair is not necessary if the air leak does not continue.

This paper presents a case of rupture of the left mainstem bronchus not associated with the factors known to cause rupture of the trachea. Large airway rupture rather than peripheral parenchymal alveolar rupture must be suspected following endotracheal intubation when subcutaneous emphysema develops and progresses rapidly and precedes signs of pneumothorax.

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Succinylcholine Administration—Another Contraindication?

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High serum potassium levels have been documented in patients with massive trauma,[1] burn injuries of skeletal muscles,[2] and neuromuscular disorders involving loss of motor function with resultant atro-

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phy.[3] The present case reports a hyperkalemic response to succinylcholine with transient ventricular dysrhythmia in a patient with wasting of thigh muscles secondary to chronic arterial insufficiency.

Report of a Case

A 56-year-old male patient was scheduled for revisions of an aortic bifurcation graft. Twelve years prior to admission the patient had resection of an abdominal aortic aneurysm. He developed ischemia of the right leg 1 year following the surgery, and an embolectomy was performed. The patient was asymptomatic for 4 years after embolectomy, but then gradually developed intermittent claudication in the right leg. Three months prior to admission he developed claudication in the left leg.

On examination, positive findings included absence of dorsalis pedis and popliteal artery pulses in both legs with slight atrophy of the right thigh muscles. Neurologic examination was normal, and the patient was able to walk two to three blocks before developing claudications. Patient was not on any chronic drug therapy including digitalis, diuretics or potassium supplements.

The patient's height was 158 cm and weight was 68 kg. Preoperative urinalysis was within normal limits; hemoglobin was 13.4 gm/100 ml and serum electrolytes were as follows: sodium, 136 mEq/L; potassium, 3.8 mEq/L; chloride, 104 mEq/L. The patient was premedicated with amobarbital sodium, 100 mg, morphine sulfate, 8 mg, and atropine sulfate, 0.4 mg IM, 1 hour prior to the anticipated time of surgery. Upon arrival in the operating room, electrocardiographic leads were applied and heart rate and Lead II electrocardiogram were continuously monitored on the oscilloscope. Blood pressure was continuously monitored by arterial cannulation with an appropriate transducer. After preoxygenation, anesthesia was induced with thiopental sodium, 300 mg IV, and 2% enflurane in oxygen. Succinylcholine, 100 mg, was administered intravenously. At this time, the electrocardiogram (ECG) revealed normal sinus rhythm. One minute following the administration of succinylcholine, the ECG revealed occasional ventricular premature beats with tall T waves which suddenly changed into ventricular bigeminy. At this time, the trachea was intubated and heparinized blood was drawn from the left radial artery and the right femoral vein for serum potassium determination. Ventricular bigeminy disappeared in 30 seconds without treatment, and the further course of anesthesia was uneventful. Serum potassium levels by flame photometer were 7.1 mEq/L in the left radial arterial sample and 12.4 mEq/L in the right femoral venous sample. Arterial pH and blood gas tensions were within normal limits.

Discussion

Cardiac dysrhythmias and cardiovascular collapse following administration of succinylcholine due to hyperkalemia have been documented in patients with massive trauma,[1] burns,[2] neuromuscular diseases,[3] and renal failure.[4] Hyperkalemia following succinylcholine in patients with neuromuscular diseases has been attributed to denervation hypersensitivity of the muscle fibers causing intracellular potassium to egress into interstitial and intravascular compartments.[5] In our patient, though there were no neurologic deficits, wasting of thigh muscles secondary to chronic arterial insufficiency was present. The chronic arterial insufficiency may have affected the vasa nervorum thereby causing minimal neural damage and secondary muscular atrophy. When succinylcholine was administered, the hypersensitive right thigh muscles released large amounts of potassium as evidenced by a serum potassium level of 12.4 mEq/L in the blood drawn from right femoral vein. The serum potassium concentration of 7.1 mEq/L in the left radial artery was due to admixture of blood with a serum potassium of 12.4 mEq/L from the right femoral vein with normokalemic blood from the rest of the body in the right atrium and right ventricle. This hyperkalemic blood perfusing through the coronary vessels might have precipitated ventricular premature beats and ventricular bigeminy.

Pretreatment with nondepolarizing muscle relaxants before the administration of succinylcholine has been shown to attenuate the efflux of potassium from the muscles in normal patients.[6, 7] In patients with neuromuscular disease or trauma, in spite of pretreatment with nondepolarizing muscle relaxants prior to succinylcholine administration, efflux of potassium is also only attenuated, not prevented.[1, 3, 7] Thus, pretreatment with a nondepolarizing relaxant might not have completely protected this patient from efflux of potassium following succinylcholine administration. In the absence of an indication for "crash" induction, a nondepolarizing relaxant would appear indicated for endotracheal intubation in patients with muscle wasting secondary to arterial insufficiency.

The incidence of hyperkalemia following succinylcholine administration in patients with generalized arteriosclerotic disease has not been reported, but arteriosclerotic disease with muscle wasting may be another contraindication to the administration of succinylcholine.

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letters TO THE EDITOR

More on Calculation of Mean pH Values

To the Editor:

I note with interest the conjunction of Dr. Harris' excellent article on variation in statistical analysis (Anesth Analg 57:322–327, 1978) with the criticism of statistical analysis of pH data (Anesth Analg 57:380–381, 1978) by Drs. Giesecke, Beyer, and Kallus, and the reference to the letter from Dr. Krause (Anesth Analg 57:143–144) on a similar topic.

Dr. Harris clearly explained how the variability of data values can be assessed by the use of the coefficient of variation, which is the standard deviation of a number of values (assumed to be taken from a population that is normally distributed) divided by the mean of those values. He also illustrated the normal and other distributions.

Both of the letters suggest that in order to analyze pH data correctly, it is necessary to correct these values into [H+]. This is not necessarily so. This procedure would only be correct if the distribution of [H+] values were normal. If this were true, then the logarithmic transform (pH) would not be normally distributed. Unfortunately there seems to be no reason to suppose that this assumption is correct for gastric secretions. If Drs. Giesecke, Beyer, and Kallus were to plot a frequency histogram for the data they manipulated, they would find that neither pH nor [H+] appears normally distributed. In fact, the coefficient of variation for the pH values (less than 60 minutes) is 0.526, which is better than the coefficient of variation for the [H+] values, which is 1.258! Dr. Baraka and his coworkers were correct in their paper when they used the chi-square test, which does not assume normal distribution of pH values (Anesth Analg 56:642–645, 1977).

Dr. Krause states that pH values will have a lognormal distribution. This is not correct. Gaddum[1] suggested that the term lognormal should be used to describe a quantity whose logarithm was normally distributed.

Dr. Krause means that [H+] is normally distributed and that pH values will be distributed logarithmically, but does not attempt to substantiate this possibility. From the Henderson equation, [H+] is the proportion of two variables that are also commonly assumed to be normally distributed:

$$[\mathrm{H}+] = \text{constant} \cdot \frac{P_{\mathrm{CO_2}}}{[\mathrm{HCO_3^-}]}$$

Consequently [H+] will have the properties of a proportion, and its logarithm, pH, would be normally distributed.[2] The conversion of a measurement into its logarithm to allow statistical analysis is a well-known and accepted technic, and I can see no reason why this procedure should not be applied to [H+] if the resultant distribution of pH values is normal.

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Penicillin Neuropathy

To the Editor:

Much in the literature indicates that penicillin has a toxic effect on nervous tissue. Convulsions occur following intraventricular administration[1] and its application directly to animal cerebral cortex has induced seizures.[2] Cerebral degeneration[3] and myeloradiculitis[4] have occurred from intrathecal administration. Although rare, peripheral neuritis has been reported as a complication of penicillin therapy.[5]

A 30-year-old physician received a penicillin injection in the right gluteal region for "strep throat" with subsequent negative throat culture. Five days later he began to have gluteal pain radiating to the posterior thigh to just below the popliteal fossa. Examination revealed a markedly restricted straight leg raising test (Lasègue's sign) with production of radiating pain. The right ankle reflex was depressed, but no motor or sensory loss was evident. Tenderness (Valleix's points) was present on palpation along the sciatic nerve. The injection site was clearly away from the nerve, and was slightly bruised.

Laboratory tests were normal; these included heterophile agglutination test ("Mono spot"), fluorescent treponemal antibody-absorption (FTA-ABS), and hepatitis-associated antigen (HAA). Sedimentation rate was 25 mm/hour (Westergren) (normal-less than 20 for males). The pain and symptoms resolved in 1 week with bed rest and analgesics; there was no recurrence in 18 months.

We believe this represents a sciatic neuritis associated with intramuscular penicillin therapy. This has been reported in a single case in 1946, but with other mononeuropathies also occurring.[5] It does not appear to be due to direct injury to the nerve by the injected material.

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Halothane Mutagenicity

To the Editor:

Dr. Ferstandig[1] in his review of the potentially toxic effects of low concentrations of anesthetic gases concluded that the levels of anesthetic gases found in unscavenged operating rooms should be nontoxic to operating room personnel. Unfortunately, data not available to him indicate that the widely used anesthetic, halothane, can give rise to mutagenic metabolites and in our opinion these data indicate that the community of anesthesia professionals should redouble their efforts to make their operating rooms free of waste anesthetic gas pollution.

In his review, Dr. Ferstandig referred to studies which indicated that halothane and a number of other anesthetics did not exhibit mutagenic activity in the Ames test. This test is a bacterial assay, developed by Bruce Ames and his co-workers at the University of California, Berkeley, and it has become the most widely used screening method for the detection of potentially carcinogenic chemicals. The test, which is quick and inexpensive compared to animal studies, monitors a chemical's mutagenic effect on bacteria. Since deoxyribonucleic acid (DNA) is similar in all living organisms and since mutation occurs by alteration of DNA, any chemical that causes mutation in one species is likely to do so in all species unless the organism can detoxify the substance before it affects the DNA. It is believed that somatic mutations are an initiating event in human carcinogenesis. It now seems that the apparent lack of halothane-mediated mutagenicity in the Ames test may be due to either the insensitivity of the test to some halothane metabolites or the failure to generate these metabolites in the test system. Cohen et al[2] have studied the pathways of halothane metabolism in humans and have suggested that 2-bromo-2-chloro-1,1-difluoroethylene (BCD) is an intermediary metabolite. Garro and Phillips[3] have reported that BCD induces mutations in both the Ames Salmonella test and a direct DNA mutagenesis assay. Furthermore, investigators at Stanford have found that a second halothane metabolite, 1,1-difluoro-2-chloroethylene is also mutagenic in the Ames test and that BCD also can be generated nonmetabolically from halothane exposed to the soda lime in carbon dioxide absorption cannisters.

There is also a recently completed study which indicates that long term exposure of animals to low concentrations of halothane in combination with nitrous oxide does result in genetic changes in both somatic and germ cells. Coate et al[4] of Hazelton Laboratories under contract to the National Institute for Occupational Safety and Health (NIOSH) examined bone marrow and spermatogonial cell populations in rats exposed to halothane, 1 part per million (ppm), concurrently with nitrous oxide, 50 ppm (twice the NIOSH-recommended limit), or halothane, 10 ppm, with nitrous oxide, 500 ppm (the average of unscavenged operating rooms). The results showed a dose-dependent increase in cytogenic aberrations in both bone marrow and spermatogonial cells' populations as well as a reduction in ovulation and implantation efficiency at the higher level of exposure and a retardation in fetal development at both levels of exposure. The simultaneous exposure to two anesthetic agents more accurately mimics human experience and brings up the problem of multifactorial etiology. It has been repeatedly demonstrated in many species, including humans, that exposure to more than one genetically active material can have synergistic effects on morbidity.

The NIOSH exposure limits were set so that they would be achievable with reasonable effort and currently available technology. It is not possible to state at this time whether an adequate margin of safety is encompassed within them. It seems reasonable that despite contradictions found within the literature that in view of the suggestive evidence cited above, we should strive for minimal exposure to waste anesthetic gases.

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book REVIEWS

A Concise Handbook of Respiratory Diseases, by Sattar Farzan, Englewood Cliffs, NJ, Prentice-Hall, Inc, 1978, 286 pp., $16.95.

This monograph was prepared specifically for respiratory therapists, nurses and other allied health practitioners who are engaged daily in the management of patients with respiratory diseases. It was pointed out in the preface that of the many texts about pulmonary disease, very few have been written at a level comprehensible to the "non-physician" in respiratory services. The goal of this book was to prepare material which would be readable, understandable and concise, but complete. At first glance, it might seem that these objectives are impossible to meet and that "concise but complete" are mutually exclusive.

Fortunately, Sattar Farzan was able, very successfully, to provide understandable synopses of many "medical" afflictions of the lung. Chapters on infectious diseases, tuberculosis, fungal infections, COPD, asthma and sarcoidosis, as well as on other problems of this variety are understandable and well written. Each chapter concludes with a current bibliography which includes excellent review articles and important references. This reading list is valuable not only for respiratory therapists and nurses but for selected medical students and house staff as well.

Chapters of the book which deal with physiologic principles and practices, however, are neither clearly written nor easily understandable. Topics such as pulmonary function and blood-gas and acid-base analyses are confusing, at best. True, clarity and brevity are difficult to achieve when physiologic concepts are being presented. The "terminal" chapters of the book deal with respiratory failure and its management. A conceptually unique approach separates respiratory failure into two types: ventilatory vs hypoxemic. While this concept seems appropriate for differentiating the patient with COPD in acute failure from the patient with classic Adult Respiratory Distress Syndrome, as the chapter proceeds, it becomes increasingly difficult to determine which type of respiratory failure is being discussed. We are cautioned on several occasions against an indiscriminate use of oxygen while treating the patient with . . . ARDS (?).

Sections dealing with mechanical ventilation are superficial. Continuous expiratory distending pressure (PEEP and CPAP) are only briefly mentioned. Little time is spent discussing the concept of PEEP titration and is limited to the suggestion that the best lung compliance indicates the most useful PEEP level.

This first edition suffers from a lack of necessary editing, and spelling and grammatical errors abound. Likewise it is disturbing that appropriate symbols for arterial blood gases are not consistently used throughout the book. Anesthesiologists may find Dr. Farzan's views on anesthesia somewhat disquieting; he writes in his chapter on cardiopulmonary arrest and resuscitation, "Situations commonly known to result in sudden and unexpected cardiopulmonary arrest include coronary artery disease, asphyxiation, anaphylactic reactions, electrical shock and general anesthesia."

In summary, the strengths of this book revolve around its clear synopses of "medical" respiratory diseases while its weaknesses are in its description of the physiology of acid-base, blood-gases, and management of respiratory failure. While this book would be of little value to the physician involved in the practice of anesthesia, it may be of some limited value to the respiratory therapist and nurse for whom it is ostensibly intended.

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The Regulation of Respiration During Sleep and Anesthesia, edited by Robert S. Fitzgerald, Henry Gautier, and Sukhamay Lahiri, New York, Plenum Publishing Corp., 1978, 448 pp., $39.50.

This book, Volume 99 in the series *Advances in Experimental Medicine and Biology* contains the papers presented at the satellite meeting on respiratory control which preceded the International Physiological Society Congress held in Paris, 1977. Many of the world's investigators in this field, including some of the most distinguished, participated, and the good quality and up-to-date nature of this book attest to the excellence of the symposium.

The papers presented concern many aspects of respiratory regulation, and these have been divided into four sections: the influence of sleep and anesthesia, the influence of the peripheral chemoreceptors, and finally the nature of the central interaction involved in respiratory control. Thus the title of the book is misleading in that only a portion of the papers presented concern this aspect of respiratory regulation, but this should not detract from the value of the book to the anesthesiologist since the subject matter as a whole is of critical importance to our field of medicine.

There are 15 papers dealing with the effects of sleep and anesthesia on respiratory control mechanisms. The following is a very brief review of some of the findings and contents presented in this section. Hugelin finds that respiratory related units extend up to the medial thalmus and that these may vary in their sensitivity to barbiturates. Some respiratory related units, contrary to previous expectations, have their excitability increased by Nembutal. Lugaresi and colleagues present their timely review on their detailed study of the sleep apnea syndrome, the clinical importance of which is now being increasingly recognized. These investigators also find that patients with COPD hypoventilate when asleep. Haddad and group report their study on normal infants when asleep. Several papers report research on the effects of sleep on the behavior of the diaphragmatic and intercostal respiratory muscles. Rehder presents an excellent review on how anesthesia with and without muscle paralysis alters respiratory mechanics and hypothesizes that altered chest wall behavior could be responsible for the decreased functional residual capacity found in the anesthetized state by many investigators. Goldman and colleagues report their study on using magnetometers to measure lung volumes. Using this apparatus, they were unable to elicit a fall in functional residual capacity with anesthesia. This finding contrasts with that of Derenne and associates who did observe a fall in functional residual capacity with anesthesia using magnetometers. The latter investigators also find that the sigh frequency is increased by anesthesia and that the expiratory time but not inspiratory time is dependent on lung volume. They suggest that this latter finding probably accounts for the ventilatory depression observed with positive-end-expiratory pressure. Manawadu and Swanson report their investigation with the use of hyperventilation during anesthesia to produce apnea thus negating the use of muscle relaxants. Knill and colleagues present their clinically important finding that, whereas both halothane and thiopental depress the hypercapnic respiratory response, halothane but not thiopental, completely abolishes the ventilatory response to hypoxia.

The book includes many more papers worthy of study. Each paper is well referenced and this will be of added value to those wishing to study further the subject presented. This book therefore is not a fireside novel, but an excellent reference source on current investigations into the regulation of respiration. Consequently it is a valuable addition to the anesthesiology department library.

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Nitroprusside and Other Short-Acting Hypotensive Agents, by Anthony D. Ivankovich, Boston, Little, Brown & Co., 1978, 318 pp.

This issue of International Anesthesiology Clinics examines various clinical drugs that the anesthesiologist may use to control blood pressure in the perioperative period. By far, the major emphasis of this book deals with intricacies of sodium nitroprusside. The anesthesiologist now has a reference source for specific questions concerning doses, hemodynamics, metabolism, and toxicity. Since these sections are all written by anesthesiologists, their discussion focuses on uses in operating room settings and by necessity, personal bias is presented. However, the more than adequate current reference list, allows the reader to sort out bias from scientific fact.

The remainder of the book deals in a chapter by chapter approach to ganglionic blocking drugs, alpha blocking agents, diazoxide, hydralazine, and intravenous nitroglycerin. These drugs are examined in terms of mechanism of action, hemodynamic effects, therapeutic indications, doses employed, metabolism, and excretion. These sections are well referenced and give the practitioner the ability to use these drugs safely.

One drug not available to all which is discussed, is intravenous nitroglycerin. Whether this agent will become a prescription drug, as is sodium nitroprusside, remains in doubt. If this agent becomes a prescription drug, Dr. Stetson's discussion will be valuable to all.

Doctor Ivankovich has done a fine job of editing the contributions from the various authors. He has limited the degree of repetition and more importantly, succeeded in getting a book of current interest into print before it has become outdated.

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Recent Advances in Intensive Therapy, edited by I. McA. Ledingham. New York, Churchill Livingstone, 1977, 257 pp., $23.00.

The field of critical care medicine is rapidly evolving and, as the editor states in his preface, "the precise role . . . cannot be assessed at this stage but data such as contained within these covers should help to provide a sound basis for future analysis." Selection of data is personal and includes 18 well written, up-to-date, and thought provoking articles whose scope is international. Individual selections are of a readable length with excellent references.

Critical care medicine is unique in several aspects: namely by creating a specialized in-hospital service to deal with a group of patients exhibiting life-threatening physiologic derangements, by using extensive and invasive monitoring as a basic adjunct to patient care, and by utilizing constant observation and feedback as the setting for decision making. The format of this volume does not reflect the unique features of intensive therapy and leaves the reader without a theoretical framework into which he may fit the individual articles.

The first concept, that of creation of an intensive therapy unit, is dealt with in the first three articles, the problem of cost effectiveness and proper utilization being discussed by J. M. Civetta. The final two articles on transportation of the intensively ill nicely supplement the idea of a specialized service for such patients. The second concept, that of monitoring, has been ignored. The third concept, that of critical care decision making, is approached indirectly by the inclusion of a number of articles written along traditional lines dealing with recent advances in understanding the pathophysiology of a number of conditions that frequently occur in the critically ill patient (i.e. massive gastrointestinal hemorrhage, coagulation disorders, Gram negative sepsis, hepatic failure). For the most part, discussion of the critically ill patient as a whole and the interaction of multiple failing organ systems with an emphasis on ongoing evaluation and reevaluation is missing. Exclusion of articles on the concepts that have set intensive therapy apart as a specialty is disappointing.

Particular attention should be paid to Chapter 7: "Acute Pancreatitis" by G. Glazer and H. Dudley. The discussion centers on a problem-oriented approach to multiple system involvement in pancreatitis with decision making occurring in the setting of appropriate patient monitoring. It illustrates well an effective approach to the critically ill patient and is a refreshing contrast to the more classically written articles.

The volume as a whole is interesting reading especially in view of the great diversity of authors, but it does not capture the unique qualities to be found in critical care medicine.

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Respiratory Therapy Pharmacology, by Joseph L. Rau, Jr., Chicago, Year Book Medical Publishers, Inc., 1978, 149 pp.

This text appears to be an accumulation of lectures which could be presented by an instructor. The subject matter is divided into appropriate topics and is presented in a lucid easy to read style.

The book contains a concise review of the role of autonomic nervous systems in respiratory physiology and summarizes much of the recent research indicating a unified mechanism of bronchial constriction and therefore, sets the stage for the next several chapters and a modern approach to treatment. A history of the introduction of oxygen as a drug is presented. The author discusses the mode of action of theophylline in an interesting manner but the chapter suffers from a lack of discussion of the serious side effects of this drug. There is no mention of the need for obtaining serum levels to prevent potential problems. There is a discussion of corticosteroids and their adverse reactions. The chapter on cromolyn sodium presents a good description of both the indication and method of administration. Finally, the discussion on prostaglandins includes some interesting theories regarding their role in pulmonary physiology and their clinical application in respiratory therapy. The book lacks a discussion of the effects that narcotics and general anesthetics have on the respiratory system.

The book is unencumbered with tedious charts and graphs. It is written simply and practically, and should be a useful addition to the library of the respiratory therapy student and practitioner, although it does not eliminate the need for frequent referrals to comprehensive textbooks for an in-depth discussion of pharmacologic principles and specific indications.

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Extrapulmonary Manifestations of Respiratory Disease, edited by Eugene Debs Robin. New York, Marcel Dekker, Inc., 1978, 516 pp., $49.50.

This volume is one of the series on "Lung Biology in Health and Disease," edited by Claude Lenfant, Director of the Division of Lung Diseases at NIH. Collectively, the series constitutes one of the most up-to-date accounts on the subject. To some extent, it replaces the two volumes on Respiration in the *Handbook of Physiology*, published 13 years ago by the American Physiological Society. However, the replacement is not complete and the flavor is different. The intent of the Handbook was to provide "an authoritative compendium of of information on the subject for the use of serious students of the field." The objectives of this series are stated more in terms of a need for a "thorough and comprehensive review" of recent research advances rather than as a detailed and relatively complete reference source. Viewed in these terms, I consider these volumes to be of outstanding value. Doctor Robin's volume is no exception. Indeed, as Claude Lenfant says in the preface "no similar volume has ever been assembled before." As with other volumes in the series, it is a collection of 13 well-referenced sections, written by various authorities, and grouped in three parts. These deal with Molecular Oxygen, Carbon Dioxide and pH, and Systemic Alterations Produced by Lung-Modified Agents. Each section is prefaced by a most useful overview of its coverage, by Dr. Robin. The third of these sections is limited to hypersensitivity and immunologic considerations, since there is a separate volume in the series on Metabolic Functions of the Lung. The latter deals in detail with the many biologically active substances modified or produced by the lung.

Wearing my clinician's hat, I tested this book as a source of information on selected topics. For example, what is the importance of oxyhemoglobin dissociation curve shift (e.g. due to 2.3. DPG abnormalities), in the clinical setting of delivery of oxygen to a sick patient? Although this has no simple answer, much of the available information is admirably summarized by P. A. Blomberg and S. P. Balcerzak in a very interesting chapter on Blood Oxygen Transport in Humans. As an indication of the scope of the book, it is interesting to note, however, that this chapter is limited to a discussion of the mechanisms involved in the hemoglobin-oxygen equilibrium, rather than a more complete review of the materials suggested by the chapter heading.

As a second sample, I searched for a discussion of the impact of normal levels of carboxyhemoglobin in oxygen delivery in urban populations. The only reference to the subject was in the very readable and authoritative chapter on the Effects of Hyperoxia on Organs and Tissues by C. J. Lambertson. This was in the context of the use of hyperoxia as a means of managing carbon monoxide poisoning. Thus, I could find no information on the usual levels of carboxyhemoglobin to be found in a hospital population or their importance.

My third clinician's question related to the effect of respiratory alkalosis and acidosis on vital organ function and, in particular, serum potassium levels. Perhaps not unexpected, the only chapter written by anesthesiologists satisfied this component of a clinical anesthesiologist's curiosity very well indeed. E. G. Pavlin and T. F. Hornbein have written a useful chapter on Organ and Tissue Disturbances Produced by Acid-Base Abnormalities.

Thus, for the clinician interested in Respiration, who is looking for a reference source, this volume will only partially satisfy his needs. On the other hand, together with others in the series, this volume makes fascinating reading and covers considerable ground, particularly at the cellular and biochemical level. The serious student should not ignore it.

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Pulmonary Disease of the Fetus, Newborn and Child, by Emile M. Scarpelli, Peter A. M. Auld, and Harold S. Goldman, Philadelphia, Lea & Febiger, 1978, 680 pp., $54.00.

The editors have gathered an internationally renowned group of experts to complete what, to this reviewer, is the best book available on pulmonary disease in young humans. The data are up to date and are compiled in a readable and understandable manner, even for the nonexpert.

Each chapter is well documented with abundant references. The chapters are arranged logically beginning with the anatomic and physiologic basis of lung examination and respiratory pathophysiology. Next airway management, mechanical ventilation, cardiopulmonary resuscitation, and inhalation therapy are discussed in some detail paying attention to details that are both practical and useful. For instance, there is a quite useful section on contamination and sterilization of respiratory therapy equipment.

Next there is a section on anesthesia and surgery related to the infant and child. The effects of anesthetic and premedicant drugs are discussed. These data give the nonanesthetist and nonsurgeon a clearer understanding of the problems faced by their colleagues in the operating room. By being aware of their problems, nonoperating room personnel will be aware of our problem and make preparation for surgery better and easier. The section on pediatric thoracic surgery is extensive and quite helpful. The basic problems and their prevention and/or treatment are well outlined. All of us will be better prepared to provide anesthesia for thoracic procedures in young patients after reading this chapter.

Next, there is a clear discussion of the pulmonary circulation and factors which affect it. This section should be of value to anyone who must anesthetize an infant or child with congenital heart disease.

Next there is a discussion of specific disease of the upper and lower airways (bronchitis, bronchiolitis, asthma) and then cystic fibrosis. There are many practical tips for treatment of these patients. The principles espoused are based on a sound physiologic background when data are available.

There are two chapters on pulmonary infections of the newborn and child including tuberculosis. Pulmonary infections are often present in patients coming to surgery. Thus, these chapters should be examined carefully by the anesthesiologist.

There then follow several chapters on lung disease in the newborn and a chapter on neonatal intensive care. The latter chapters will give the reader a good understanding of the problems related to homeostasis which these patients often have (temperature, electrolytes, glucose, etc.). An understanding of these principles will improve the care of neonates coming for surgery.

Finally there is a chapter on uncommon diseases and another on pediatric pulmonary radiology. The latter is well laced with clear pictures of radiographs and a clear description of the findings and interpretation. This chapter on Radiology will certainly be of help in understanding the disease processes and their effects on lung function and pulmonary circulation.

This book is well written, enjoyable, and useful. I feel it should be read by any anesthetist who cares for children whether full- or part-time.

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BOOK NOTES

1978 Yearbook of Anesthesia, edited by James E. Eckenhoff, Chicago, Year Book Medical Publishers, Inc., 1978, 352 pp.

The Year Book of Anesthesia, 1978, follows the format of previous years and presents a carefully selected group of abstracts sorted into 23 general areas. A statement in the table of contents informs the reader that the material covered represents review articles up to November 1977. There are frequent editorial notes which add to the value of the abstracted information by keeping them in perspective. The index is adequate, but the volume could use a summary of the journals from which the abstracts were gleaned.

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Relief of Intractable Pain, Second Edition, edited by Mark Swerdlow, Amsterdam, Elsevier-North-Holland Publishing Co., 1978, 340 pp. $61.25.

In this completely revised second edition, there has been a great deal of updating in all the chapters. In particular, the chapters on nerve blockings and large fiber nerve stimulation methods have been expanded.

Both the neurophysiologic explanation of the conditions involved and the relevant complications are detailed throughout the text. The book is comprehensive, authoritative, and practical. It will be the reference text for many years to come for all those who are interested in managing the patients with intractable pain.

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BOOKS RECEIVED

Practical Anesthetic Pharmacology, edited by Attia Rafik R, Grogono Alan W, New York, Appleton-Century-Crofts, 1978, 293 pp.

Research in Pediatric Surgery, edited by Bill AH, Boix-Ochoa J, Ferguson CC, et al, Baltimore, MD, Urban & Schwarzenberg, 1978, 214 pp., $24.50.

The Caval Catheter, by C. Burri and F. W. Ahnefeld, New York, Springer-Verlag, 1978, 84 pp., $14.00.

1978 Yearbook of Anesthesia, edited by James E. Eckenhoff, Chicago, Year Book Medical Publishers, Inc., 1978, 352 pp.

Biological Foundations of Biomedical Engineering, edited by Jacob Kline, Boston, Little, Brown & Co., 1976, 988 pp., $37.50.

Pulmonary Disease of the Fetus, Newborn and Child, by Emile M. Scarpelli, Peter A. M. Auld, and Harold S. Goldman, Philadelphia, Lea & Febiger, 1978, 680 pp., $54.00.

Relief of Intractable Pain, Second Edition. edited by Mark Swerdlow, Amsterdam, Elsevier-North Holland Publishing Co., 1978, 340 pp., $61.25.

Long-Term Infusion of Thiopental

Thirty patients requiring prolonged mechanical ventilation received continuous infusions of sodium thiopental as the only sedative agent. Thiopental was administered for 2 to 14 days at a dose of 103 ± 32.1 mg/hour (mean ± SE). Plasma levels approximated 15 μg/ml. Hemodynamic measurements, including cardiac output, were obtained with the use of arterial (30 patients) and pulmonary artery (27 patients) catheters. With the exception of decreased heart rates during thiopental infusion, none of the hemodynamic or respiratory variables studies were significantly altered. The technique proved effective and safe for patients requiring either controlled ventilation or intermittent mandatory ventilation. (*Carlon GC, Kahn RC, Goldiner PL, et al: Long-term infusion of sodium thiopental: hemodynamic and respiratory effects. Crit Care Med 6:311–316, 1978*)

Low Dose Heparin

In a randomized, double-blind trial, 5000 USP units of sodium heparin or saline were given subcutaneously at least 2 hours before surgery and at 12-hour intervals thereafter to patients requiring total hip replacement, surgical correction of hip fracture, or lower extremity amputation for vascular insufficiency. Lung perfusion scans were performed before surgery and at weekly intervals during the postoperative period. Pulmonary arteriograms were obtained in patients developing new perfusion defects on serial scans. Two hundred twelve patient hospitalizations were analyzed. Acute pulmonary embolism was diagnosed by serial lung perfusion scans or at autopsy in 37 patients. The incidence of pulmonary embolism in 40 patients with below the knee amputation was too low to warrant conclusions. The incidence of acute pulmonary embolism in 94 patients undergoing above the knee amputation was 25% in patients receiving heparin and 27% in patients receiving saline. The incidence of acute pulmonary embolism in 78 patients undergoing hip surgery was 13% in patients receiving heparin and 12% in patients receiving saline. The regimen used had no significant effect on the incidence of acute pulmonary embolism in patients undergoing hip surgery or above the knee amputation. (*Williams JW, Eikman EA, Greenberg SH, et al: Failure of low dose heparin to prevent pulmonary embolism after hip surgery or above the knee amputation. Ann Surg 188:468–474, 1978*)

Perioperative Myocardial Infarction

Myocardial injury during a variety of cardiac surgical operations was determined in 57 patients by serial electrocardiograms (ECGs), serial determinations of serum creatine phosphokinase (CPK), and perioperative and postoperative technetium-99m stannous pyrophosphate (PYP) scans. ECG evidence of injury developed in four patients, whereas positive localized injury by PYP scan developed in 10. Twenty-one patients had elevated CPK enzymes postoperatively. The localization of injury by PYP scan correlated with ECG evidence of infarction in only one of four patients. Localized left ventricular injury by PYP scan without new Q waves on the ECG was common (5 of 12) in patients undergoing aortic valve replacement with perfusion of the coronary arteries. The injury in patients with congenital heart disease occurred at sites of ventricular incision or suggested possible air embolization of the coronary arteries. Perioperative infarction is frequently segmental and nonstransmural and occurs in patients with coronary, valvular, and congenital heart disease. (*Young DJ, Utley JR, Damron JR, et al: Results and patterns of perioperative myocardial infarction. J Thorac Cardiovasc Surg 76:528–532, 1978*)

Endocarditis with Pulmonary Artery Catheters

The postmortem finding of acute right-sided bacterial endocarditis in a burn patient monitored with an indwelling pulmonary artery (Swan-Ganz) catheter for 14 days prompted a review of autopsies of burn patients in whom a pulmonary artery catheter had been used. Autopsies of six consecutive burn patients monitored with a pulmonary artery catheter revealed septic or aseptic endocarditis. In two of the six patients, right-sided staphylococcal endocarditis was the anatomic cause of death. In the remaining four, the lesions were aseptic thrombotic vegetations involving primarily the right atrium, tricuspid valve, right ventricle, and pulmonic valve. In the severely burned patient, factors that may combine with the presence of the foreign object to favor develoment of endocarditis include intermittent bacteremia, hypercoagulability, hyperdynamic cardiovascular function, and the use of antibiotics resulting in resistant strains. While an indwelling pulmonary artery catheter can provide useful monitoring information, it is sometimes responsible for serious complications in burned or septic patients. *See Also*—Editorial. Watanakunakorn C: Infective endocarditis as a result of medical progress. Am J Med 64:917–919, 1978. (*Ehrie M, Morgan AP, Moore FD, et al: Endocarditis with the indwelling balloon-tipped pulmonary artery catheter in burn patients. J Trauma 18:664–666, 1978*)

Anesthesia in Multiple Sclerosis

One hundred patients followed by a Multiple Sclerosis (MS) Clinic provided information about prior anesthetic experiences. Forty-two patients underwent 88 general anesthetics. In only one patient was there evidence of MS relapse. This incidence is thought compatible with the natural history of MS. Eight patients reported 12 episodes of spinal or caudal anesthesia, with a 10% incidence of MS relapse. Data for spinal anesthetics, although limited, are in keeping with previous reports. The authors found no evidence to suggest that general anesthesia precipitated relapses or increased the rate of progression of disability. They caution that temporary fluctuations of MS symptoms can occur postoperatively in MS patients due to the known effects of fever and metabolic imbalance upon nerve transmission. These fluctuations should not be unjustly attributed to general anesthesia alone, nor should they be confused with MS relapses or progression of disability. (*Bamford A, Sibley W, Laguna J: Anesthesia in multiple sclerosis. Can J Neurol Sci 5:41–44, 1978*)

Atropine and Mucociliary Transport Rates

A radioactive tracer method of measuring mucociliary transport rates (MCTR) in vivo was used in dogs. A small volume of a suspension of radio-labeled albumin microspheres 5 to 7 μm in diameter is deposited on the mucosal surface at the carina via a catheter placed through the inner channel of a bronchoscope. The rate of movement of these spheres toward the larynx is visualized sequentially by means of a gamma scintillation camera with a large field of view and is recorded as polaroid images. Using this technique, transport rates were determined in the tracheas of 10 anesthetized dogs (17 experiments) before and 10 minutes after IV injection of 0.4 mg of atropine sulfate. Each animal served as its own control. Baseline MCTR values were determined by using microspheres labeled with 140-kev technetium-99m. After infusion of atropine, MCTR values were determined using microspheres labeled with 390-kev indium-113m. Because of their widely differing energy spectrums, both test agents could be used in rapid succession by adjusting the spectrometer of the scintillation camera. MCTR increased in 13 experiments, did not change in two, and decreased in two. The percentage increase in MCTR after infusion of atropine was significant as compared to baseline values (30.0 ± 0.6%, mean ±SE; $p < 0.05$). The effect of atropine in improving mucociliary clearance was quantitatively similar to that previously reported for beta-adrenergic agonists. (*Chopra SK: Effect of atropine on mucociliary transport velocity in anesthetized dogs. Am Rev Respir Dis 118:367–371, 1978*)

Ventilator Circuit Changes and Infection

The relationship between frequency of ventilator circuit changes and risk of ventilator-associated pneumonia was studied using two independent approaches. The first was an in-use aerosol contamination study with patients on 8-hour, 16-hour, or 24-hour ventilator changing schedules. The second approach was a study comparing the incidence of pneumonia in patients on ventilators for two 1-year periods when the ventilator circuit changing time differed. In-use aerosol sampling of 513 ventilator treatment periods showed bacterial contamination greater than 100 organisms per aerosol in 1.8% of 8-hour cycles, in 2.5% of 16-hour cycles, and in 5.4% of 24-hour cycles. These differences were not significant. The incidence of ventilator-associated pneumonia was the same for 1-year periods when ventilator circuits were changed either every 8 or every 24 hours. It was concluded that changing ventilator circuits every 24 hours provides adequate protection from ventilator-associated pneumonia. (*Lareau SC, Ryan KJ, Diener CF: The relationship between frequency of ventilator circuit changes and infectious hazard. Am Rev Respir Dis 118:493–496, 1978*)

Effect of Tidal Volume and PEEP on Compliance

In 12 patients requiring therapy with mechanical ventilation for acute respiratory failure, total static compliance (Cst) increased from 29 ± 4 ml/cm H_2O at a tidal volume (TV) of 5 ml/kg to 42 ± 7 ml/cm H_2O at a TV of 15 ml/kg. Similarly, Cst increased from 42 ± 7 ml/cm H_2O to 52 ± 8 ml/cm H_2O between 0 and 6 cm H_2O of positive end-expiratory pressure (PEEP). At high levels of pulmonary inflation (i.e. high PEEP and large TV) compliance decreased. The changes of total respiratory compliance with TV were mainly due to changes in pulmonary compliance. With PEEP, the functional residual capacity increased, and specific compliance did not change. Two mechanisms may be responsible for the changes in compliance. First, varying TV or PEEP will alter the position of tidal ventilation on the pressure-volume curve, resulting in an increase in compliance with increasing TV and PEEP up to a point, where overdistention occurs and compliance decreases. Second, the function of the surface tension lowering substance may be altered in acute pulmonary parenchymal disease, thus disturbing the regulation of surface tension over the range of pulmonary inflation studied. (*Suter PM, Fairley HB, Isenberg MD: Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. Chest 73:158–162, 1978*)

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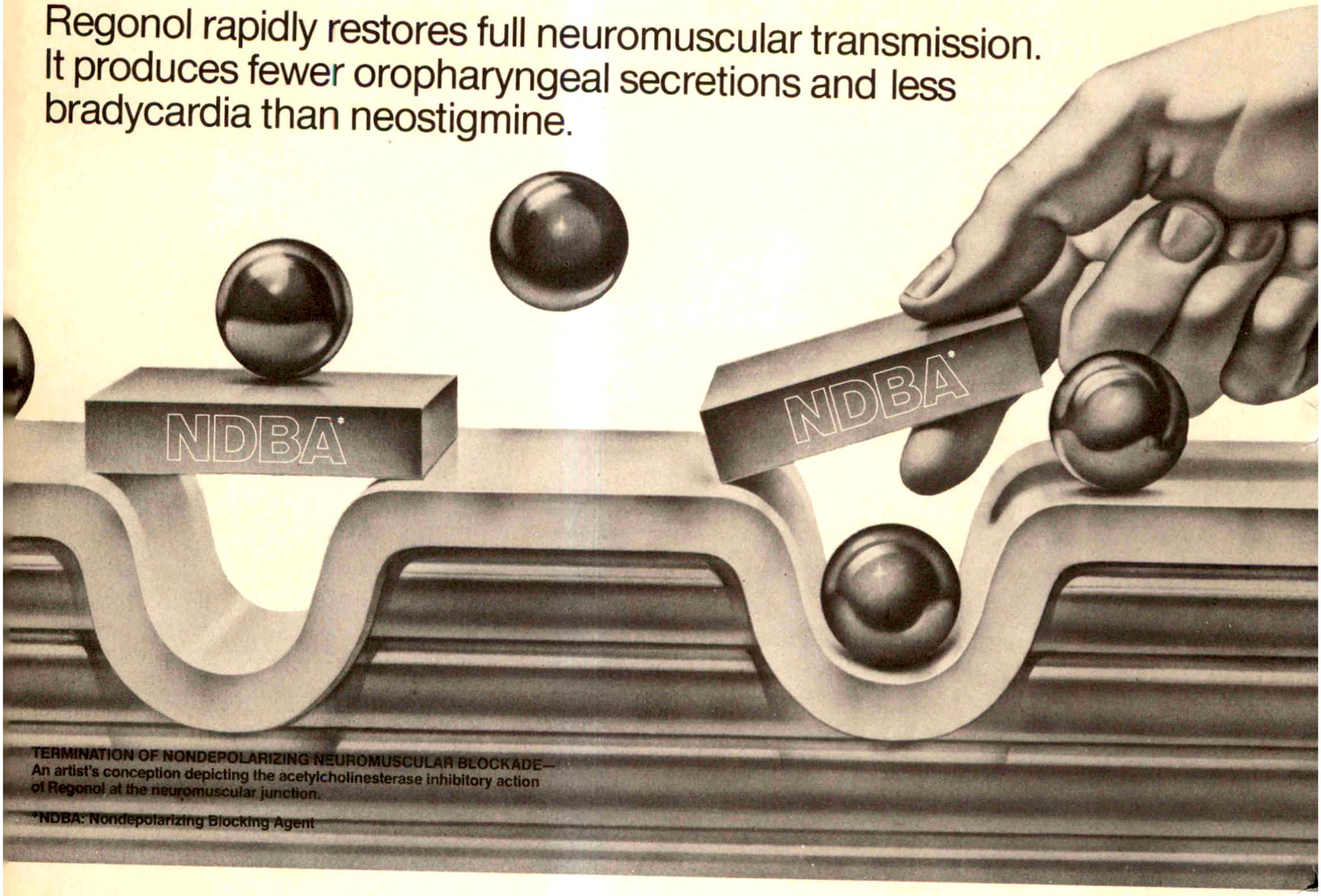

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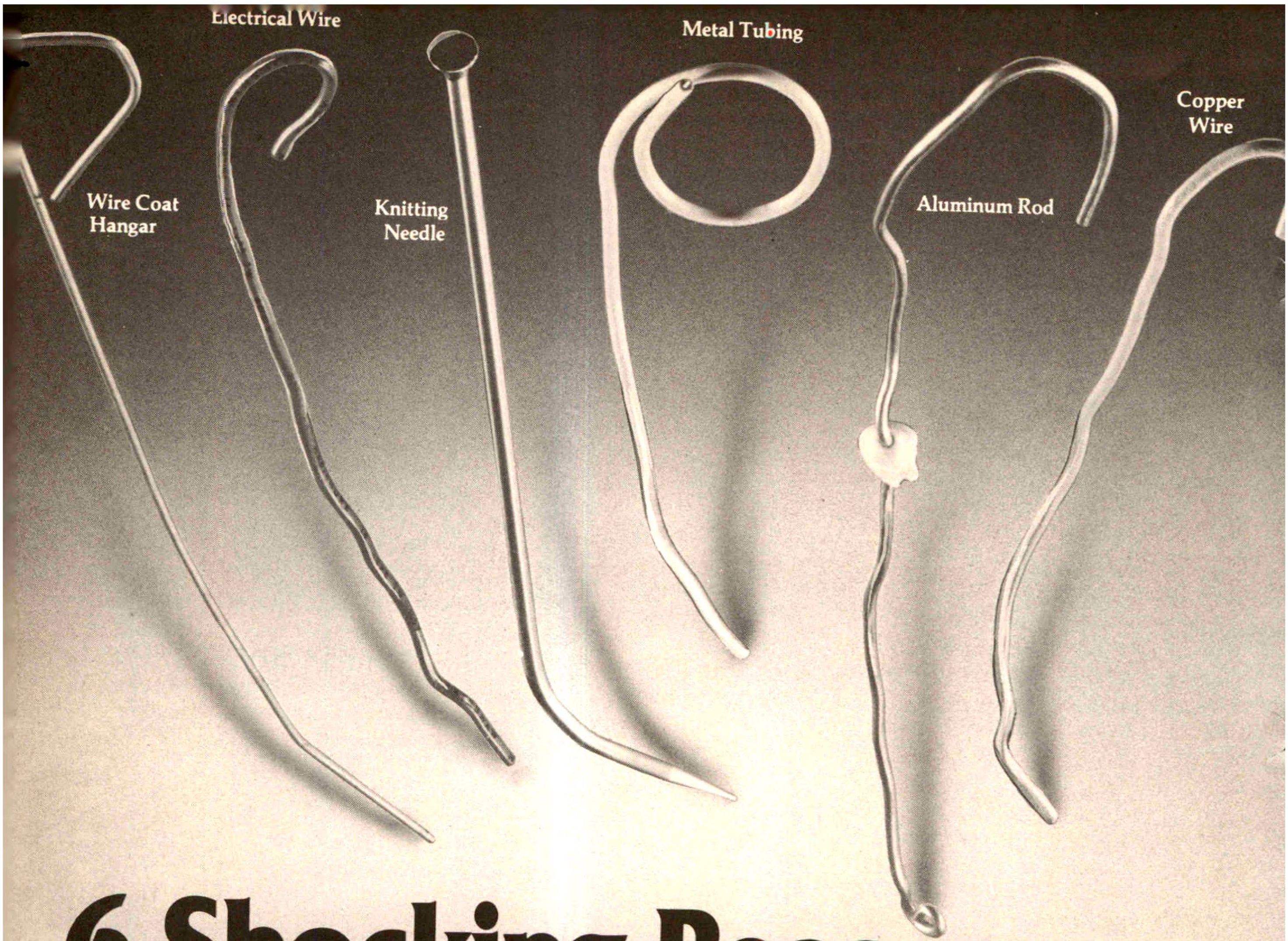

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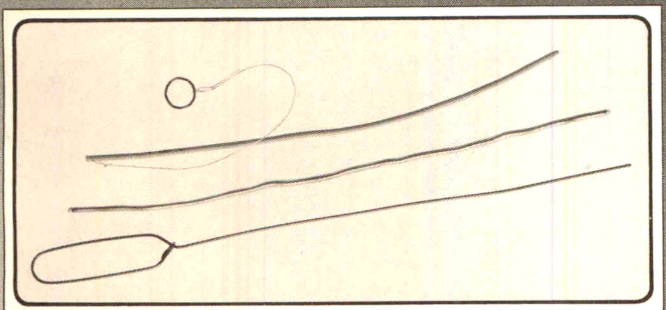

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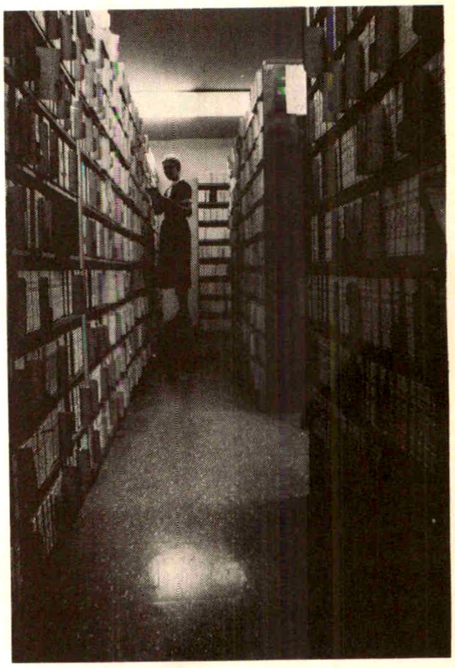

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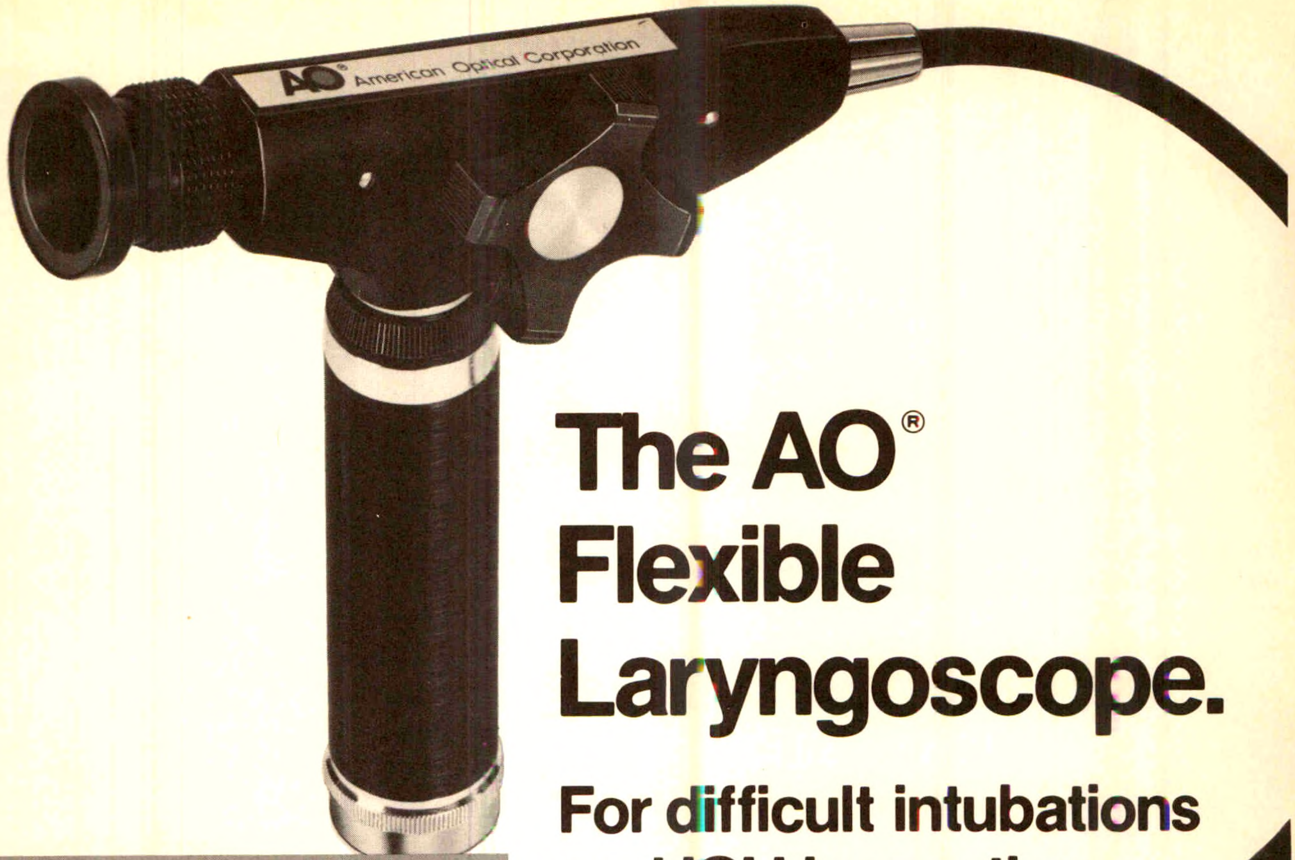

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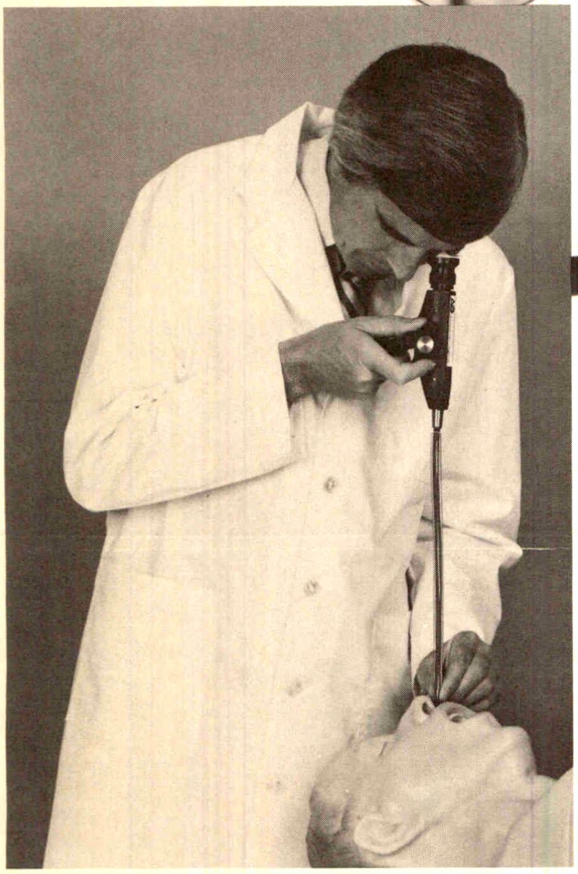

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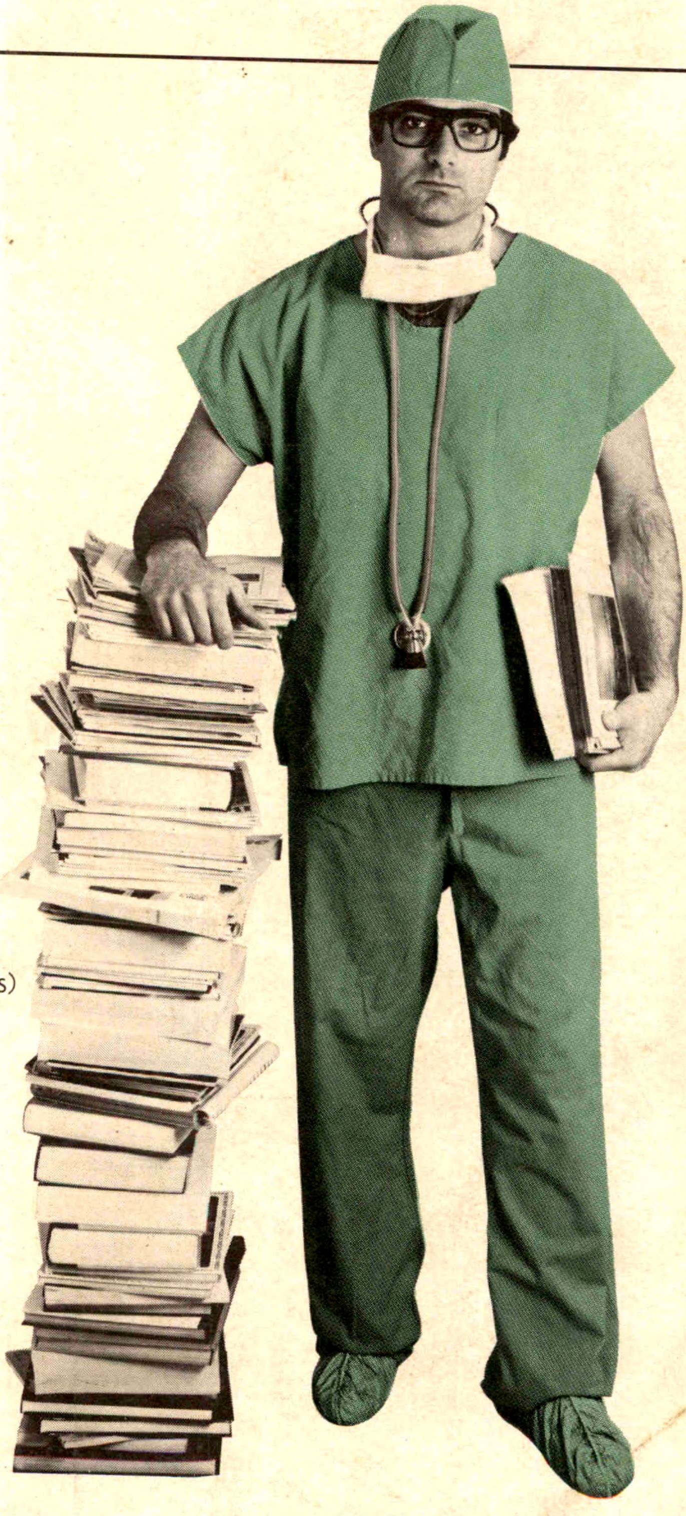

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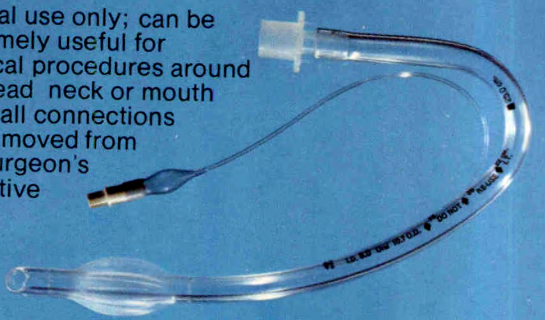

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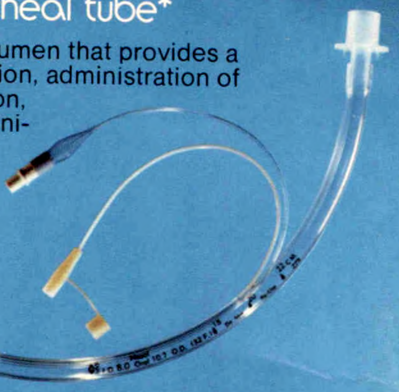

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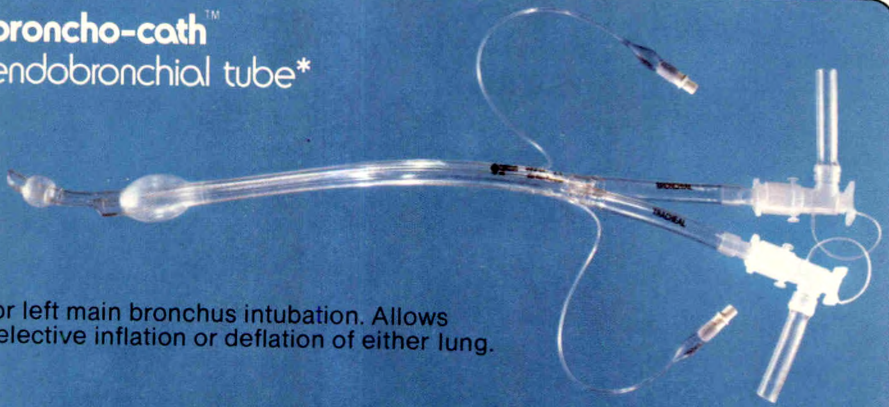

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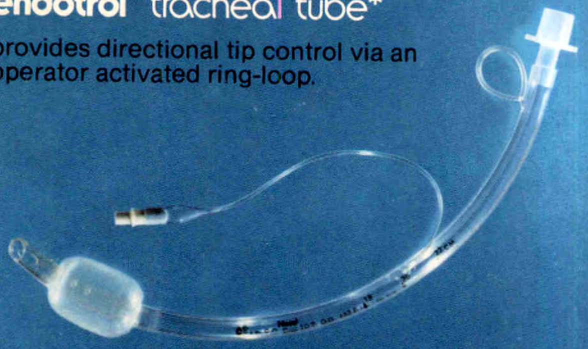

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ERRATUM 142

Selected cases for Ketalar

There are certain situations where the advantages of Ketalar suggest its serious consideration. Four such hypothetical situations are detailed here.
A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.

Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).

Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgical anesthesia (generally within three to four minutes) at a range of 9 to 13 mg/kg, with the effect lasting from 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burn patients (particularly helpful in children where the veins are small). IM administration is also convenient and effective for repeated short-term anesthesia for such procedures as changing burn dressings, and skin grafts.

advancement in anesthesiology
Ketalar
(Ketamine HCl injection)
Parke-Davis

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;
2. for the induction of anesthesia prior to the administration of other general anesthetic agents;
3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension

(ketamine HCl inj) . . . and a caution

Manipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must be moved freely, and in which the maintenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be transferred from a supine to an upright, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.

Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.

A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

DOSAGE AND ADMINISTRATION

Preoperative Preparations:

1. While vomiting has been reported following Ketalar administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, since these reflexes may also be diminished by supplementary anesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketalar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.
2. Atropine, scopolamine, or other drying agent should be given at an appropriate interval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

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Brief Summary (Please consult full package insert, enclosed in every package, before using Pavulon).

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

Reference:
1. Stanley and Liu, Anesth Analg 56:669, 1977

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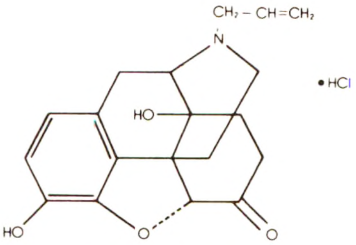
DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



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(-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

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ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ±5 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

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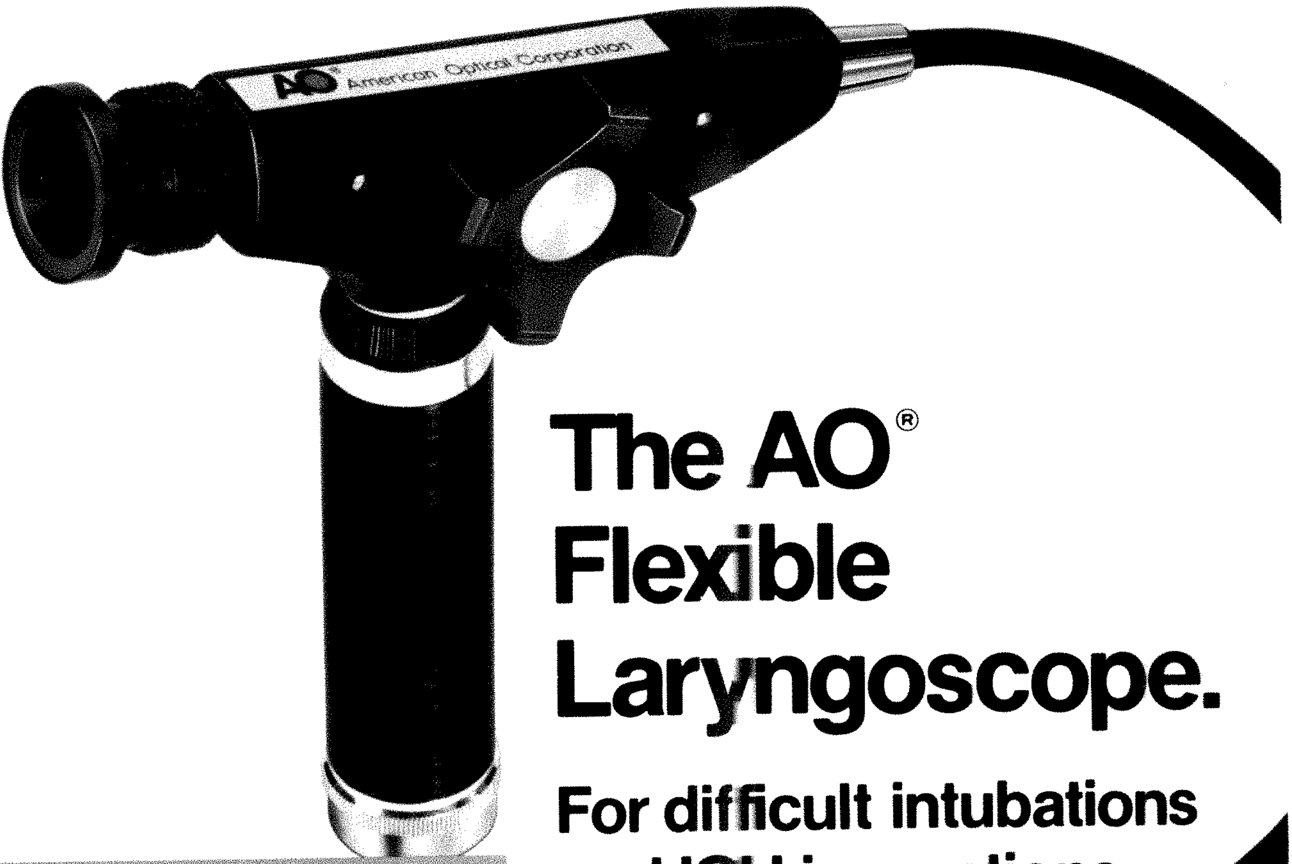

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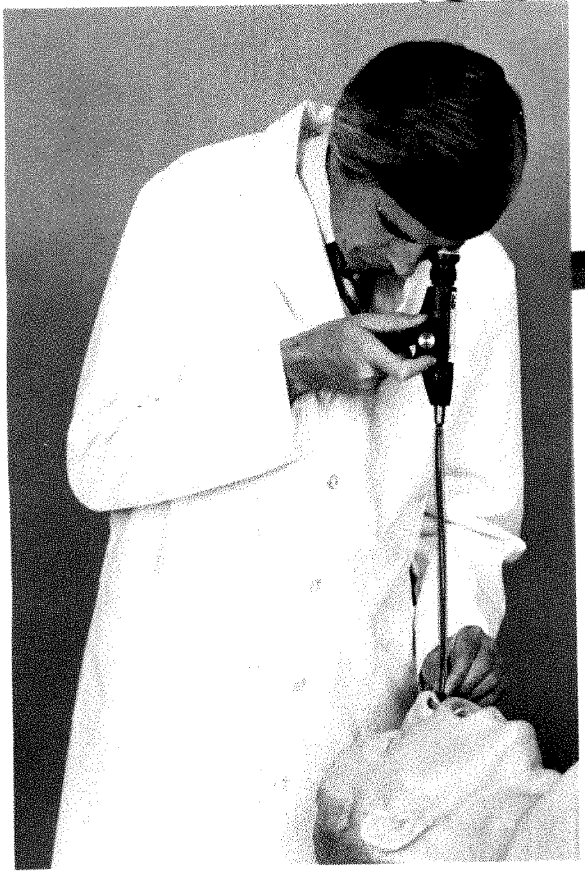

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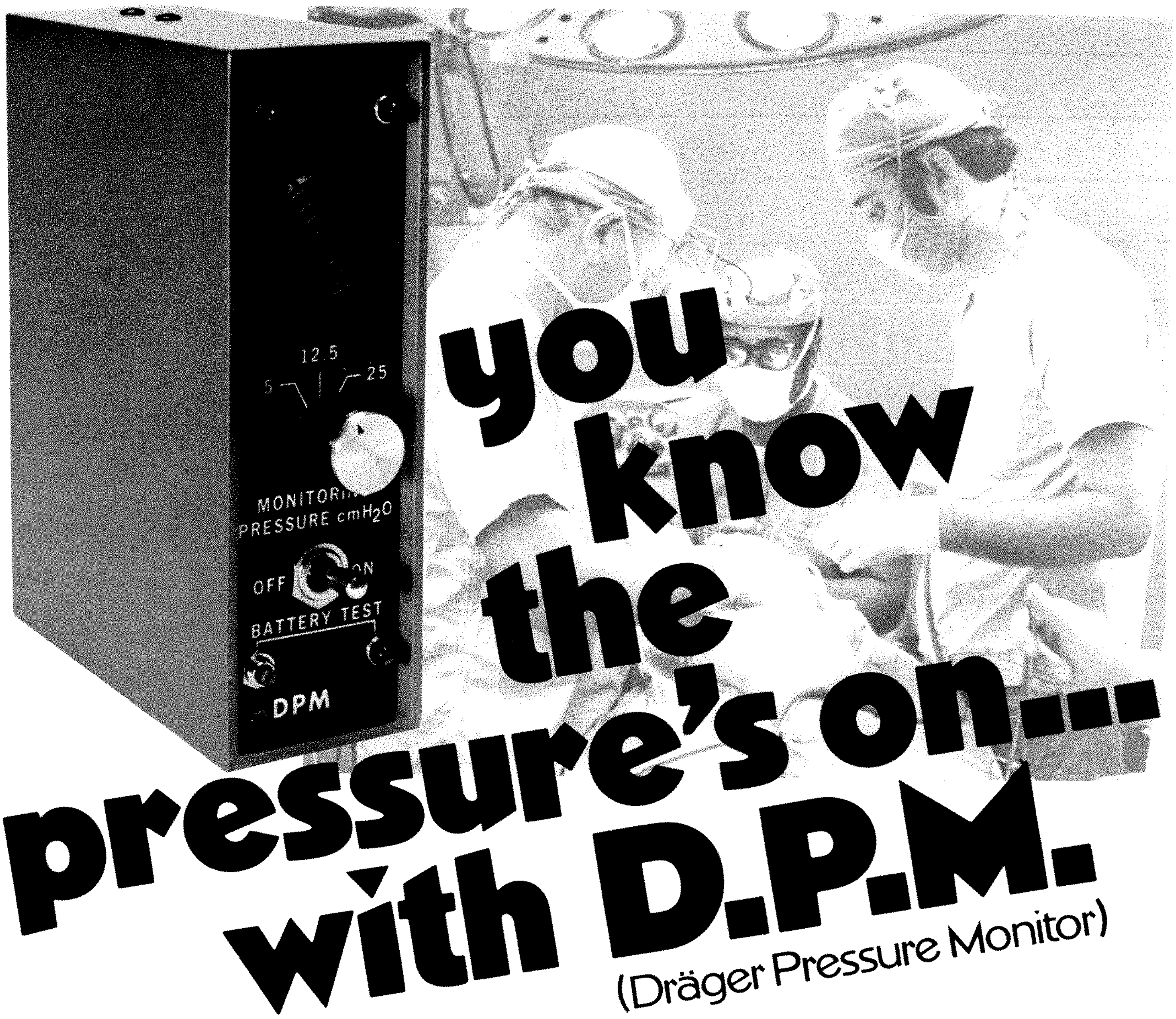
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Now, an anticholinergic for use in anesthesia with significant advantages over atropine...

Robinul® Injectable

(Glycopyrrolate Injection, NF)

- Little or no CNS effect
- Prolonged vagal blocking effect
- Longer antisialagogue activity

See last page for

PRE-OPERATIVELY

- Protects against excessive pharyngeal and bronchial secretions.
- Protects against excessive volume and acidity of gastric secretions—a danger if pulmonary aspiration occurs.
- Protects against vagal reflexes at time of intubation.

INTRA- OR POST-OPERATIVELY

- Protects against arrhythmias and bradycardia associated with drugs used for reversal of muscle relaxants (e.g. neostigmine).
- Protects against surgically-induced vagal reflexes.

Robinul® Injectable (Glycopyrrolate Injection, NF)

an anticholinergic with significant advantages over atropine

Situation	Objective	Action
preoperative	Reduction of gastric secretions plus elevation of gastric pH above 2.5 to help protect against serious sequelae of aspiration.	Use Robinul Injectable in the premedication regimen.
induction of anesthesia	To have unobstructed view of glottis prior to tracheal intubation. To help protect against vagal reflexes during intubation.	Use Robinul Injectable in the premedication regimen.
intra-operative	To help protect against surgically or drug induced vagal reflexes.	Use Robinul Injectable intraoperatively.
post-operative	To help prevent excess peripheral muscarinic effects of cholinergic agents used in the reversal regimen.	Use Robinul Injectable in the reversal regimen.
recovery room	To help prevent "central anticholinergic syndrome."	Use Robinul Injectable whenever an anticholinergic is used.

Each 1 ml contains:

Glycopyrrolate, NF	0.2 mg
Water for Injection, USP	q.s.
Chlorobutanol, USP (preservative)	0.5%

For intramuscular or intravenous administration in conjunction with anesthesia.

Contraindications: There are no absolute contraindications to the use of Robinul Injectable in conjunction with anesthesia except known hypersensitivity to glycopyrrolate.

Warnings: This drug should be used with great caution, if at all, in patients with glaucoma or asthma.

Precautions: *Usage in Pregnancy.* The use of any drug in pregnancy, lactation, or in the childbearing age requires that the potential benefits of the drug be weighed against the possible hazards to mother and child. Reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate. However, diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

Use with caution in patients with: myasthenia gravis; coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertension.

The intravenous administration of any anticholinergic in the presence of cyclopropane anesthesia can result in ventricular arrhythmias; therefore, caution should be observed if Robinul (glycopyrrolate) Injectable must be used during cyclopropane anesthesia. If the drug is given in small incremental doses of 0.1 mg or less, the likelihood of producing ventricular arrhythmias is reduced.

Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur.

Adverse Reactions: Anticholinergics produce certain effects most of which are extensions of their fundamental pharmacological actions. Adverse reactions to anticholinergics in general may include dry mouth; urinary hesitancy and retention; blurred vision due to mydriasis; increased ocular tension; tachycardia; palpitation; decreased sweating; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestation; some degree of mental confusion and/or excitement, especially in elderly persons.

Dosage and Administration: Robinul (glycopyrrolate) Injectable may be administered intramuscularly, or intravenously, without dilution, in the following indications:

Adults: *Preanesthetic Medication.* The recommended dose of Robinul (glycopyrrolate) Injectable is 0.002 mg (0.01 ml) per pound of body weight by intramuscular injection, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Robinul (glycopyrrolate) Injectable may be used during surgery to counteract drug-induced or vagal traction reflexes with the associated arrhythmias (e.g., bradycardia). It should be administered intravenously as single doses of 0.1 mg (0.5 ml) and repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Children: *Preanesthetic Medication.* The recommended dose of Robinul (glycopyrrolate) Injectable in children up to 12 years of age is 0.002 mg to 0.004 mg (0.01 ml to 0.02 ml) per pound of body weight intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Because of the long duration of action of Robinul (glycopyrrolate) if used as preanesthetic medication, additional Robinul (glycopyrrolate) Injectable for anticholinergic effect intraoperatively is rarely needed; in the event it is required the recommended pediatric dose is 0.002 mg (0.01 ml) per pound of body weight intravenously, not to exceed 0.1 mg (0.5 ml) in a single dose which may be repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended pediatric dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Compatibility With Other Agents: *Known compatibilities.* Robinul (glycopyrrolate) Injectable is compatible for mixing and injection with the following: 5% and 10% glucose in water or saline; Demerol® (meperidine) Injectable; morphine sulfate; Innovar® (fentanyl plus droperidol) Injectable; Vistaril® (hydroxyzine) Injectable; Prostigmin® (neostigmine) Injectable; Mestinon® (pyridostigmine) Injectable. Robinul Injectable may be administered via the tubing of a running infusion of physiological saline or lactated Ringer's solution.

Known incompatibilities include the following injectables: sodium bicarbonate; Valium® (diazepam); sodium pentobarbital; various phenothiazines; Dramamine® (dimenhydrinate), and chloramphenicol.

Drug Interaction During Anesthesia. Glycopyrrolate has been used clinically with at least the following medications: a barbiturate (sodium thiopental); narcotic analgesics (morphine, alphaprodine hydrochloride, fentanyl); sedative/tranquilizers (droperidol, diazepam); gaseous anesthetics (nitrous oxide); volatile liquid anesthetics (diethyl ether, halothane, methoxyflurane, enflurane), parenteral anesthetics (ketamine); peripherally-acting skeletal muscle relaxants (succinylcholine, gallamine, d-tubocurarine, pancuronium); cholinergic agents (neostigmine, pyridostigmine); and other anticholinergics (atropine).

There are no known unique or unanticipated drug-drug interactions with other agents except that Robinul (glycopyrrolate) Injectable should be used with caution if at all during cyclopropane anesthesia (see Precautions).

Management of Overdosage: To combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulfate may be given in a dose of 1.0 mg for each 1.0 mg of Robinul (glycopyrrolate) Injectable known to have been administered.

How Supplied: Robinul (glycopyrrolate) Injectable is available in 1 ml single dose vials, and 5 ml and 20 ml multiple dose vials (NDC 0031-7890). Rev. Aug. 1976

A.H.Robins Company, Richmond, Va. 23220

A·H·ROBINS

for intramuscular or intravenous administration in conjunction with anesthesia

Robinul® Injectable

(Glycopyrrolate Injection, NF)

SIEMENS

The Lung Mechanics Calcula
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The Lung Mechanics Calculator is used for the calculation, display and recording of lung-mechanics.

The Lung Mechanics Calculator can also be used as an aid in choosing the best setting for the ventilator, and to indicate the effectiveness of the ventilator treatment.

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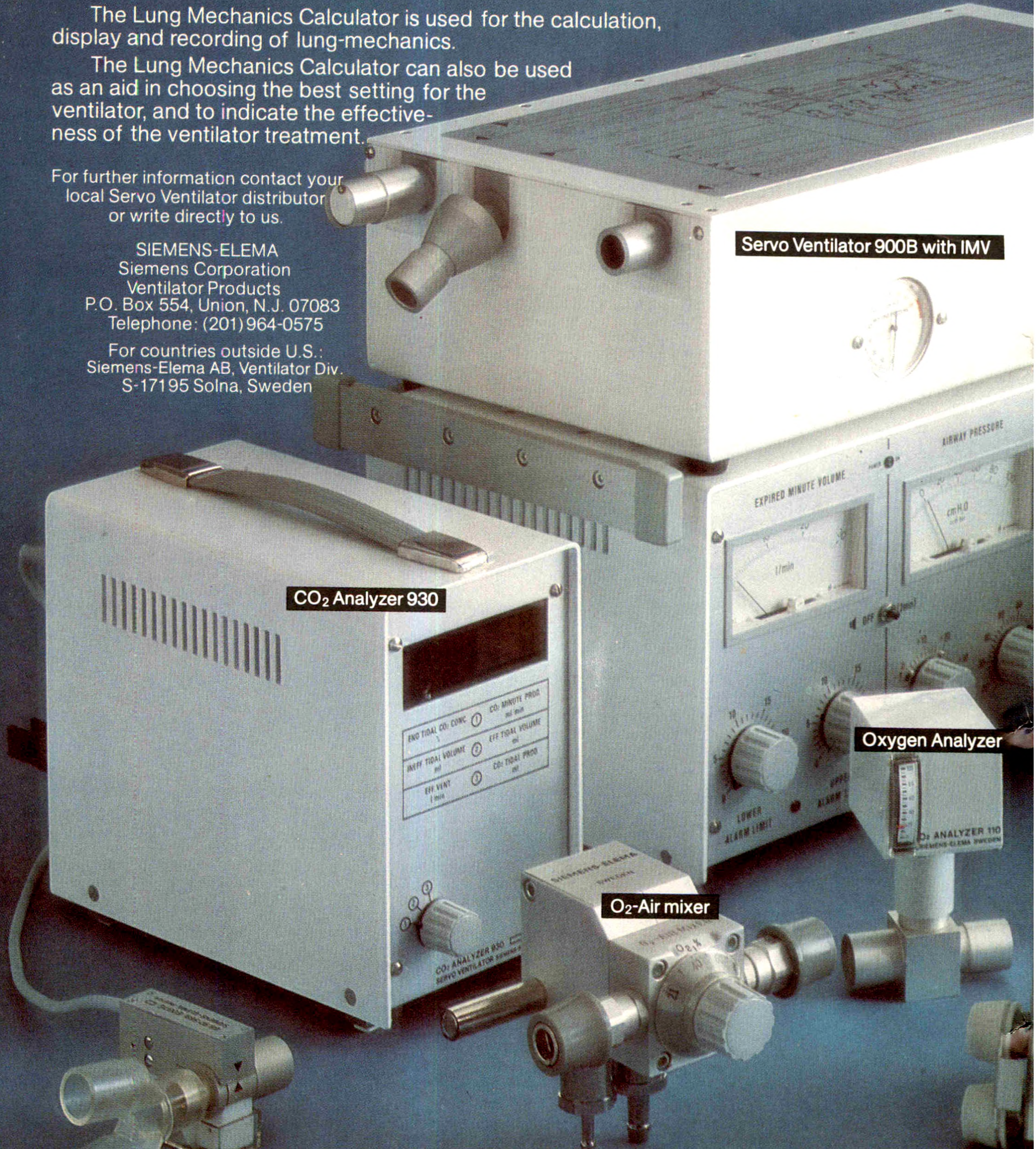

The Limitless Servo Ventilator

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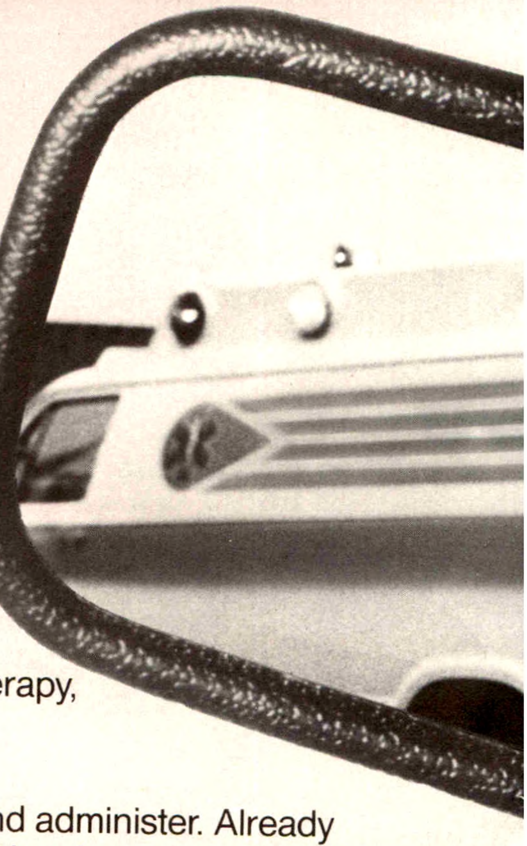
CORTICOID THERAPY IN CRITICAL CARE



Pharmacologic doses of corticoids have been used in the treatment of shock unresponsive to conventional therapy, if adrenocortical insufficiency exists or is suspected.

Differences That Count

Hexadrol® phosphate injection is easy to handle, store and administer. Already in solution, it can be used directly from the vial. Hexadrol has benzyl alcohol as a preservative and is stable at room temperature.

The multi-dose vial minimizes waste. When used in pharmacologic doses, Hexadrol offers significant savings over methylprednisolone.*

*Based on average wholesale price listings in *Drug Topics Red Book 1979*. Actual prices paid by direct purchasers will vary by order size but are usually lower for Hexadrol.

Hexadrol® Phosphate Injection

dexamethasone sodium phosphate injection USP

BEFORE PRESCRIBING OR ADMINISTERING, PLEASE CONSULT COMPLETE PRODUCT INFORMATION, A SUMMARY OF WHICH FOLLOWS:

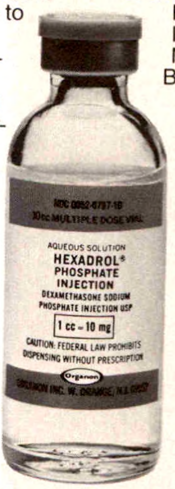
ACTIONS—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

CONTRAINDICATIONS—Systemic fungal infections—Hypersensitivity to any component.

WARNINGS—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage In Pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be nec-



100 mg

All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

PRECAUTIONS—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocu-

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, approrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

ADVERSE REACTIONS—
Fluid and electrolyte disturbances: Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

Musculoskeletal: Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

Dermatologic: Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

Neurological: Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; Increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Miscellaneous: Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

DOSAGE AND ADMINISTRATION—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.

CAUTION—Federal law prohibits dispensing without prescription.

HOW SUPPLIED—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25; 10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

Hexadrol is available in two potencies, 4mg/cc and 10mg/cc in aqueous solution with 1% benzyl alcohol as preservative.

When You Need it… Hexadrol Has It!

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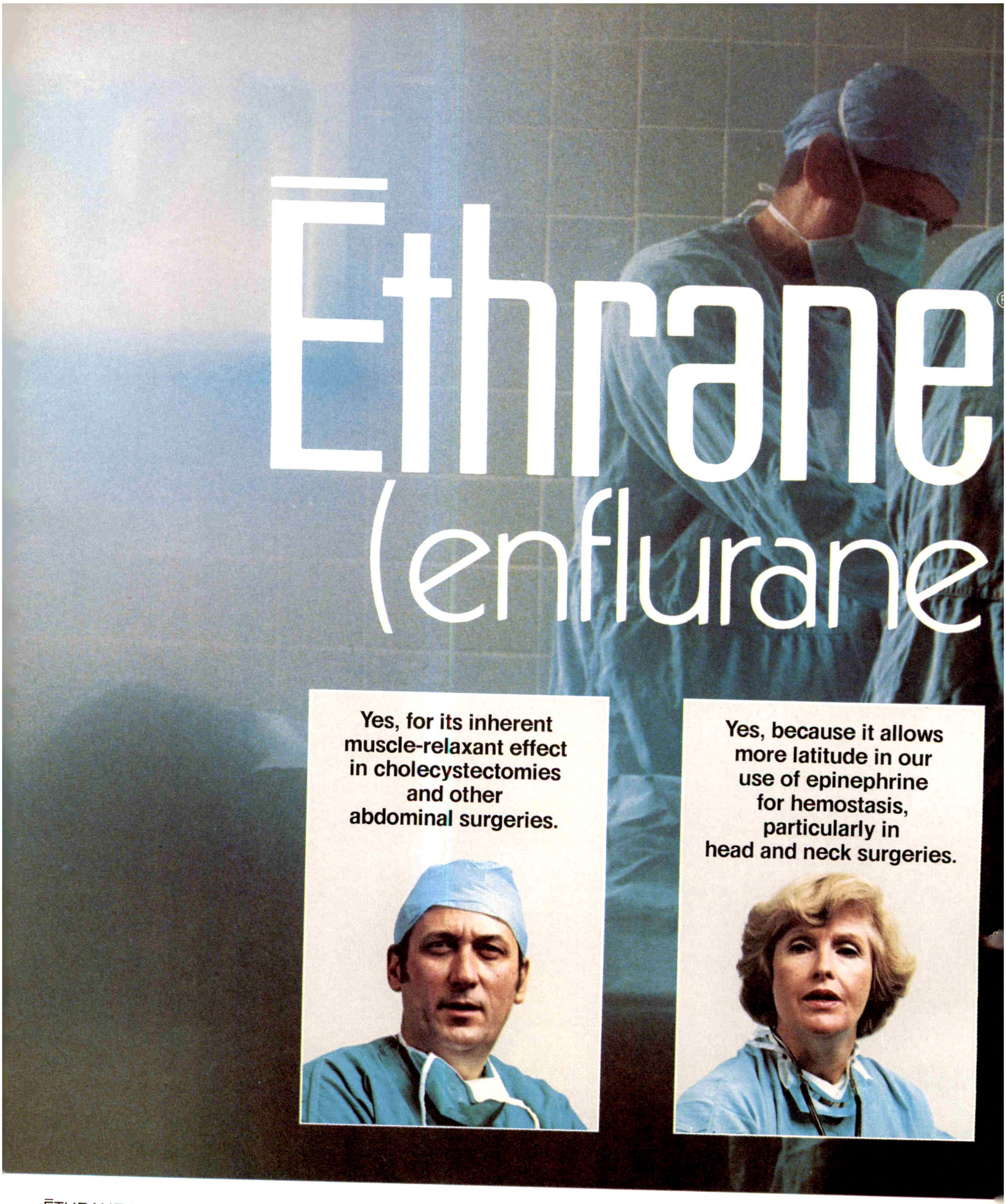


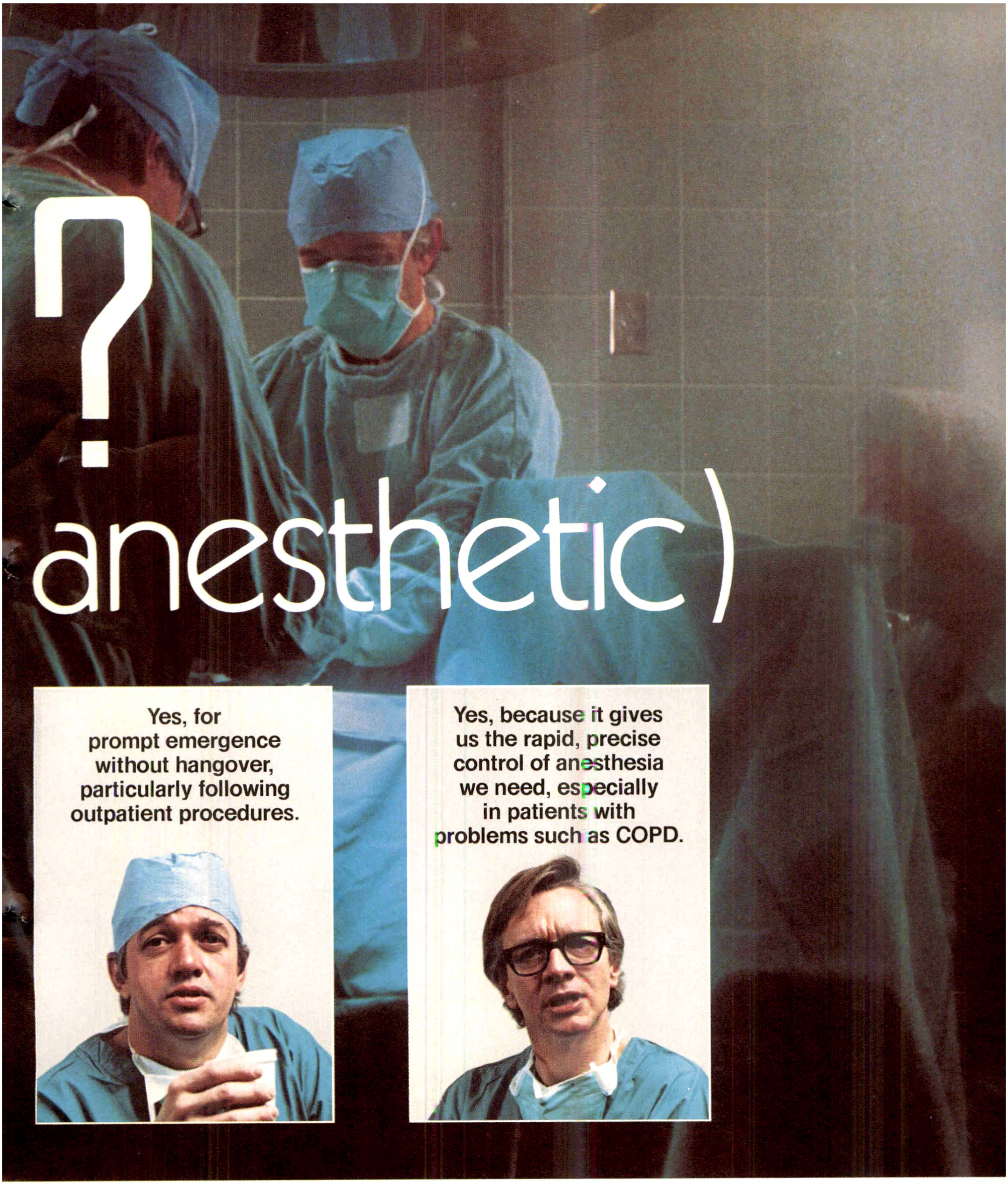
Yes, for its inherent muscle-relaxant effect in cholecystectomies and other abdominal surgeries.

Yes, because it allows more latitude in our use of epinephrine for hemostasis, particularly in head and neck surgeries.

ĒTHRANE (enflurane)—with its low solubility in blood, inherent muscle-relaxant effect, and apparent lack of cardiac arrhythmic effect—offers you and your surgeons more control and more flexibility. And for patient comfort it provides smooth, rapid inductions, prompt emergence (with no need for narcotic reversal agents), and an early sense of alertness and well-being.

Facts About ĒTHRANE (enflurane)

- Blood-gas partition coefficient—1.9 @ 37°C.
- Compatibility with epinephrine—up to three 10 ml. injections of epinephrine solution (1:100,000 or 1:200,000) may be given within an hour.
- Concomitant muscle-relaxant dosage—(if needed) only ½ to ⅓ the usual requirements of nondepolarizing agents.


?
anesthetic)
Yes, for prompt emergence without hangover, particularly following outpatient procedures.
Yes, because it gives us the rapid, precise control of anesthesia we need, especially in patients with problems such as COPD.

New ĒTHRANE (enflurane) Compendium and Reference

Virtually all of the known facts about this remarkably versatile anesthetic—along with succinctly phrased, informative clinical data—are now available to you and your staff in the new, updated *ĒTHRANE (enflurane) Compendium and Reference.* Ask your OHIO Anesthetic Agents Representative for your copy or write to us in Madison. For a summary of complete usage information, please see the following page.

Ohio Medical Products
3030 Airco Drive, Madison, Wisconsin 53707

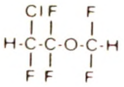
AIRCO®

Ēthrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ĒTHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$\begin{array}{cccccc} & \mathrm{Cl} & \mathrm{F} & & \mathrm{F} & \\ & | & | & & | & \\ \mathrm{H}- & \mathrm{C}- & \mathrm{C}- & \mathrm{O}- & \mathrm{C}- & \mathrm{H} \\ & | & | & & | & \\ & \mathrm{F} & \mathrm{F} & & \mathrm{F} & \end{array}$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \quad A = 7.967$$
$$B = -1678.4$$
$$T = {}^\circ C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ĒTHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ĒTHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ĒTHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

ACTIONS

ĒTHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ĒTHRANE are rapid. ĒTHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ĒTHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ĒTHRANE. ĒTHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ĒTHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ĒTHRANE anesthesia. ĒTHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ĒTHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ĒTHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ĒTHRANE.

Biotransformation of ĒTHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ĒTHRANE anesthesia in man in the absence of surgery. Thus ĒTHRANE does not depress this aspect of the immune response.

INDICATIONS

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ĒTHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ĒTHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ĒTHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ĒTHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ĒTHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ĒTHRANE.
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ĒTHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ĒTHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ĒTHRANE mixture. In general, inspired concentrations of 3.5-4.5% ĒTHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ĒTHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ĒTHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

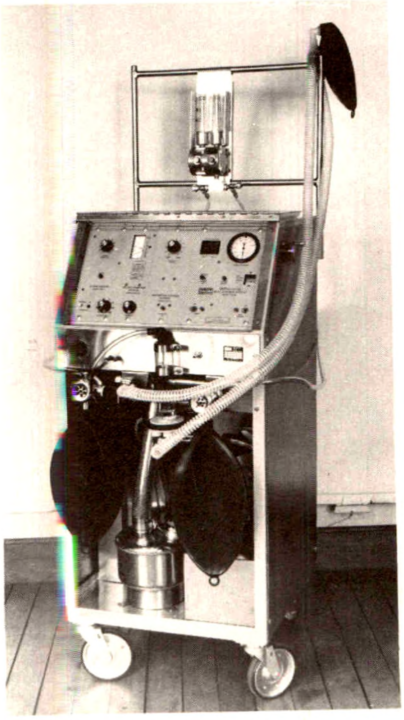
PACKAGING

ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Products
Division of Airco Inc.
P.O. Box 7550, 3030 Airco Drive, Madison, Wis. 53707
AIRCO®

EMERSON
IMV Ventilator

Intermittent Mandatory Ventilation



Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

Please request Form 3-MV.

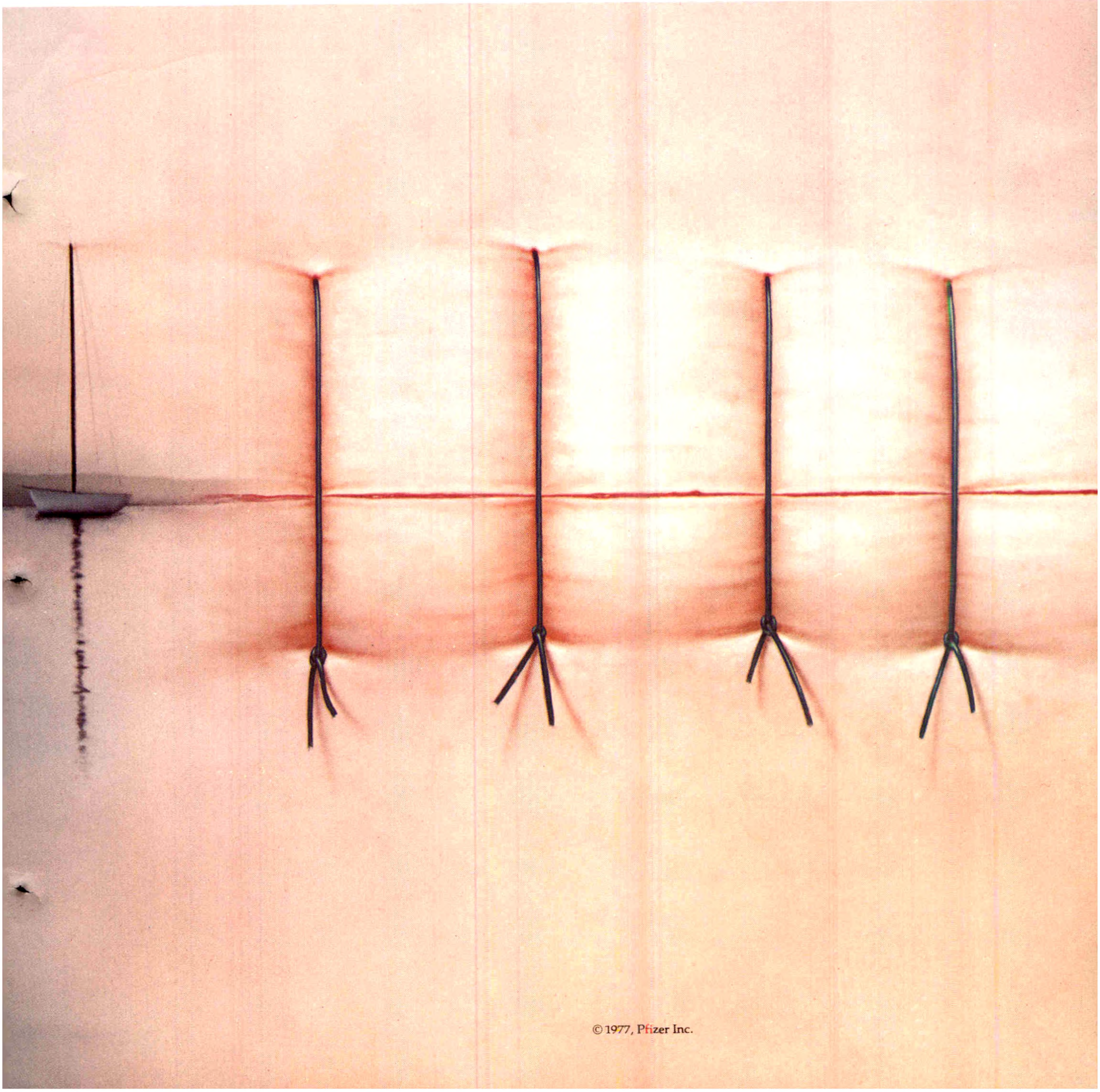
J. H. EMERSON COMPANY
CAMBRIDGE, MASSACHUSETTS 02140

The Calm introductio

to surgery

Vistaril® I.M.
(hydroxyzine HCl)
—allays anxiety
—reduces narcotic requirements
—and controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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Vistaril® I.M.
(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

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Cook County Graduate School of Medicine

announces

SPECIALTY REVIEW COURSE IN ANESTHESIOLOGY

May 13–18, 1979

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The meeting is held in the attractive and comfortable setting of the university.

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THE WORLD IS ITS PROVING GROUND

More widely investigated than any other inhalation anesthetic. Association with hepatotoxicity extremely rare.[1]

Risk of liver toxicity from the use of FLUOTHANE® (halothane, U.S.P.) has been shown to be extremely rare. Unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and...the overall safety record of the anesthetic was excellent."[1]

These are conclusions drawn from the United States National Halothane Study, a comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE.

On the basis of postoperative morbidity for all types of operations, including high risk, the incidence for FLUOTHANE was 1.87%...compared with the 1.93% average for all anesthetic procedures.[2]*

Over 450 million administrations worldwide.

More anesthesiologists throughout the world choose FLUOTHANE more often than any other inhalation anesthetic. To date, there have been well over 110 million administrations in the United States alone... for a wide variety of procedures and techniques in patients of all ages.

References: 1. Brown, B.R., and Sipes, I.G.: Commentary-Biotransformation and hepatotoxicity of halothane. Biochem. Pharmacol. 26:2091, 1977. 2. Bunker, J.P., et al: The National Halothane Study. Washington, D.C. Government Printing Office, 1969.

FLUOTHANE®

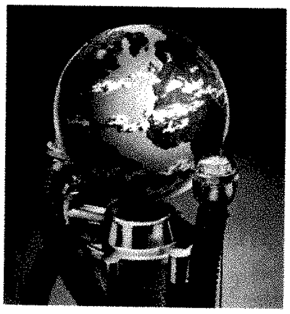
(halothane, U.S.P.)

the most widely used inhalation anesthetic in the world

Ayerst

**See following page for full prescribing information.*

the most widely used inhalation anesthetic in the world



FLUOTHANE®

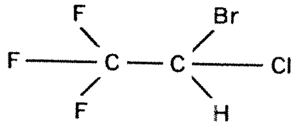
BRAND OF

halothane, U.S.P.

for patients of any age, in almost any kind of surgery

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE (halothane, U.S.P.) is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE (halothane, U.S.P.) has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w).

Ayerst® Ayerst Laboratories
New York, N.Y. 10017

7918

[illegible] just

1530 [illegible]

1803 Morphine isolated from opium

1945 Semisynthetics and synthetics gain acceptance

1967 The age of nonnarcotic analgesics dawns

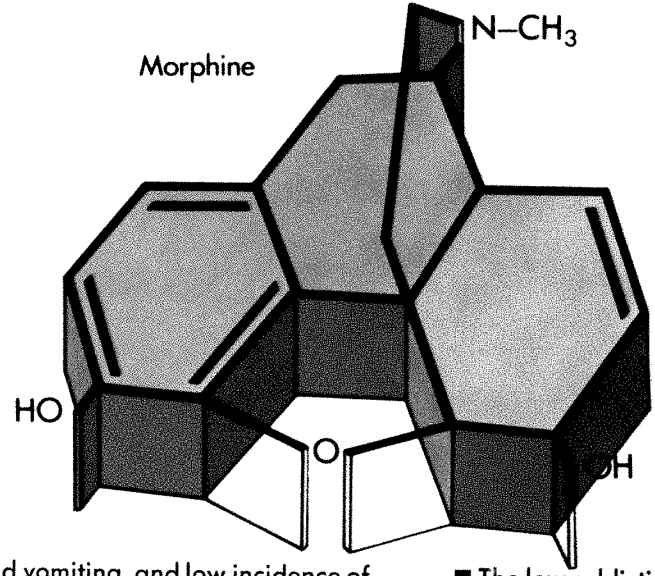
and new in...

1978

Now...
in moderate to severe pain Stadol

(butorphanol tartrate)

Bristol Laboratories is pleased to announce a new, extensively studied,[1-39] nonnarcotic, parenteral agent that comes closer to the ideal analgesic—combining a high degree of potency in the relief of moderate to severe pain, with a low potential for undesirable side effects.



Important new option when potent parenteral analgesics are indicated

■ Standard doses of Stadol are as effective in relieving pain as standard doses of both morphine[1-4] and meperidine.[5-7, 37]

■ By either I.M. or I.V. route—provides prompt onset of analgesia, achieves peak activity rapidly, maintains effects for 3–4 hours.

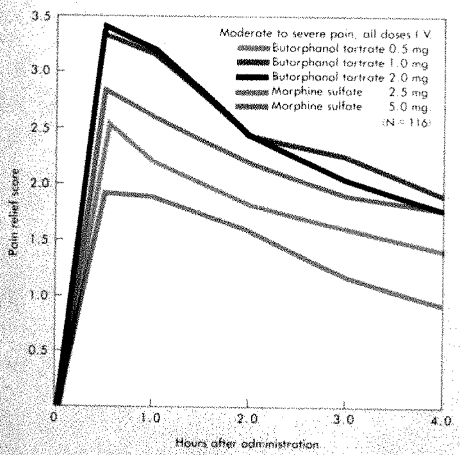
■ Distinguished by its favorable side effects profile,[1-16, 31-33, 36, 37]—low physical-dependence liability, limited respiratory depressant effect, little nausea and vomiting, and low incidence of CNS effects other than sedation.

■ 2 mg. of Stadol produces an order of respiratory depression similar to that caused by 10 mg. of morphine. In contrast to morphine, increasing Stadol doses yield greater analgesic effect,[9] without appreciably increasing liability for respiratory depression.[16]

■ The low addictive potential of Stadol[24] is underscored by its narcotic antagonist properties.

Stadol is not recommended for patients physically dependent on narcotics or with significant previous narcotic experience. Its use in such patients, without prior detoxification, will result in induction of withdrawal reactions.

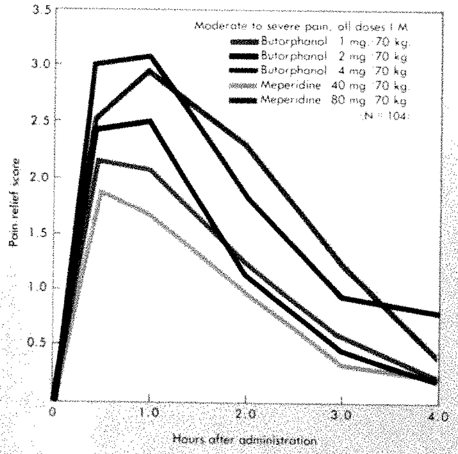
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate and morphine sulfate

In this study "... butorphanol tartrate 0.5 mg produced greater relief than morphine sulfate 2.5 mg and butorphanol tartrate 1.0 and 2.0 mg produced greater relief than morphine sulfate 5.0 mg." **(DelPizzo[1])**

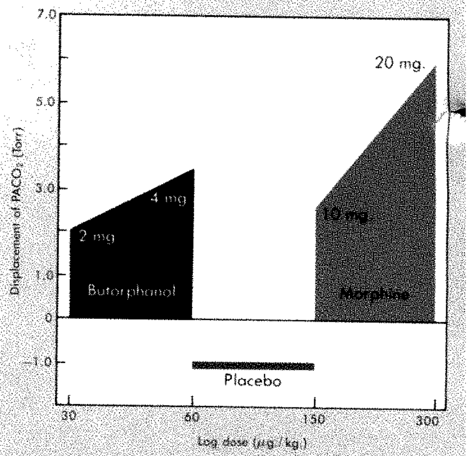
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate and meperidine hydrochloride

In moderate to severe pain, butorphanol tartrate provided relief "... that was not statistically distinguishable from that achieved with 80 mg/70 kg meperidine." **(Gilbert et al[5])**

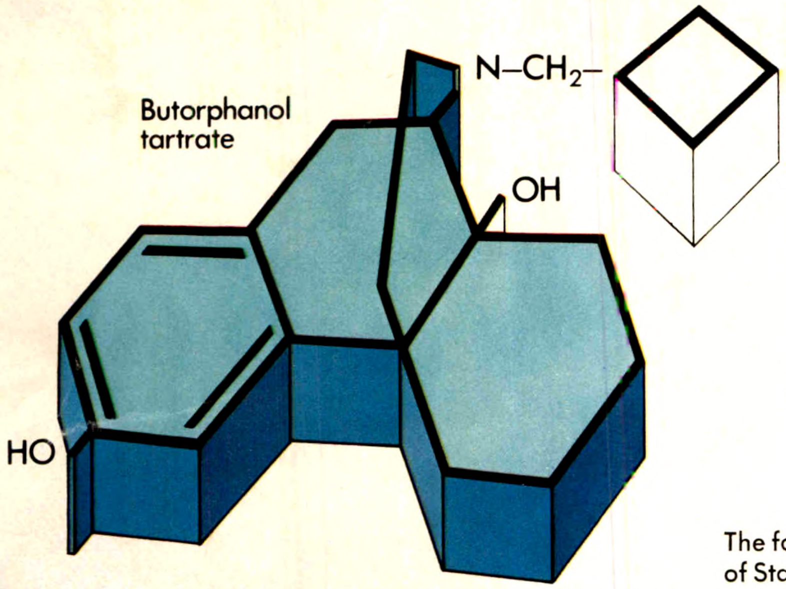
Limited respiratory depressant effect



Log dose PACO₂ displacement curves

In this graph based on alveolar carbon dioxide tension ($PACO_2$) measurements, the flatter the curve, the less respiratory depression. "The flat dose-response curve ... of butorphanol may indicate that, because of its antagonistic properties, there is a limit to its respiratory depressant effects. **(Adapted from Nagashima et al[16])**
Unlike morphine with its steep dose-response curve, the magnitude of respiratory depression does not increase in a

closer to the ideal parenteral analgesic



Butorphanol tartrate

new Stadol® IM IV

(butorphanol tartrate)

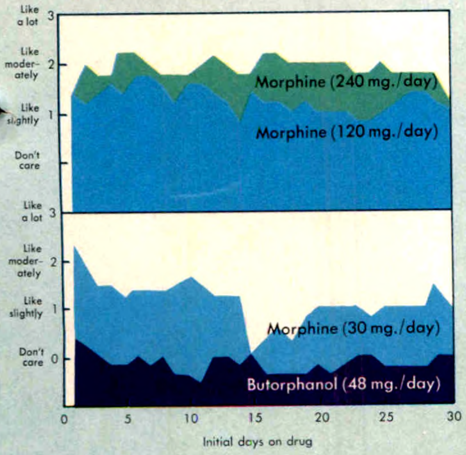
another step closer to the ideal

The following table shows a side-by-side clinical comparison of Stadol with both morphine and meperidine.

Clinical parameters	Meperidine	Morphine	Stadol
Classification	narcotic	narcotic	nonnarcotic
Indication	moderate to severe pain	moderate to severe pain	moderate to severe pain
Standard I.M. dose	75–100 mg.	8–10 mg.	2 mg. (1 to 4 mg.)
Standard I.V. dose	50–100 mg.	4–10 mg.	1 mg. (0.5 to 2 mg.)
Usual route of administration	I.M./I.V.	I.M./I.V.	I.M./I.V.
Onset of pain relief	30 minutes I.M., very rapidly I.V.	30 minutes I.M., very rapidly I.V.	less than 30 minutes I.M., very rapidly I.V.
Peak analgesic activity	within 1 hour I.M., within 30 minutes I.V.	within 1 hour I.M., within 20 minutes I.V.	within 1 hour I.M., within 30 minutes I.V.
Duration of pain relief I.M./I.V.	slightly less than morphine	about 4 hours	3–4 hours
Addicting potential	high	high	low
Respiratory effects	dose-related depression	dose-related depression	limited depression—no appreciable dose-related increase within the range of recommended doses.

Data for this table were obtained from: Jaffe, J. H. and Martin, W. R.: Narcotic analgesics and antagonists, in The Pharmacological Basis of Therapeutics (Goodman, L. S. and Gilman, A., eds.), ed. 5, New York, Macmillan, 1975, pp. 245–283; AMA Drug Evaluations, ed. 3, Chicago, 1977,

Low physical-dependence liability



Preference scores completed by subjects during chronic butorphanol tartrate administration compared with scores from three other groups of subjects receiving 30, 120 and 240 mg. of morphine daily. (Adapted from Jasinski et al[24])

BRISTOL™
BRISTOL LABORATORIES
Div. of Bristol-Myers Company

In moderate to severe pain...
New, parenteral

new Stadol® IM IV
(butorphanol tartrate)

(1) 8/18/78

INDICATIONS AND USAGE—
Stadol is recommended for the relief of moderate to severe pain.
CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.
WARNINGS—Patients physically dependent on narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.
Drug dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical-dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.
Head injury and increased intracranial pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.
Cardiovascular effects: Because Stadol increases the work of the heart, especially the pulmonary circuit (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.
PRECAUTIONS—Certain respiratory conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.
Impaired renal or hepatic function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.
Biliary surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.
Usage in pregnancy: The safety of Stadol for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.
Usage in labor and delivery: Safety to the mother and fetus following administration of Stadol during labor and delivery has not been established.
Usage in nursing mothers: The use of Stadol is not recommended in nursing mothers since it is not known whether this drug is excreted in human milk.
Pediatric use: Safety and efficacy in children below age 18 years have not been established.
ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS effects: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic effects: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision
OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.
Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors, and assisted or controlled respiration.
DOSAGE AND ADMINISTRATION—*Adults:* Intramuscular—The usual recommended single dose is 2 mg. This may be repeated every three to four hours, as necessary. The effective dosage range, depending on the severity of pain, is 1 to 4 mg. repeated every three to four hours. At this time, there is insufficient clinical data to recommend single doses beyond 4 mg.
Intravenous—The usual recommended single dose for intravenous administration is 1 mg. repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg. repeated every three to four hours.
Children: Since there is no clinical experience in children under 18 years, Stadol is not recommended in this age group.
Storage conditions: When stored at room temperature, the stability of the solution in vials is 2 years.
SUPPLY—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, 2 mg. per ml., 2-ml. vial; 1 mg. per ml., 1-ml. vial; 2 mg. per ml., 1-ml. vial; 2 mg. per ml., 10-ml. multi-dose vial.
NDC 0015-5644–2 mg. per ml., 2-ml. vials
NDC 0015-5645–1 mg. per ml., 1-ml. vials
NDC 0015-5646–2 mg. per ml., 1-ml. vials
NDC 0015-5648–2 mg. per ml., 10-ml. multi-dose vials

For information on package sizes available, refer to the current price schedule.

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EDITORIAL

It's No Laughing Matter

INHALATION is one of the simplest, most effective and rapid means of administering drugs. Since the early periods of anesthetic use when man first learned to use ether, chloroform, and nitrous oxide for hedonistic purposes, these substances and others have continued to be abused. Even though the literature abounds with statements describing the hazards of inhalant use, some substances, including the organic nitrites, aerosol paints, and N_2O, have apparently increased in popularity. Today, the dimensions of this problem are still poorly understood.

Most regional and national surveys lump the use of all volatile substances together. National reporting systems such as the Drug Abuse Warning Network (DAWN, supported by Drug Enforcement Administration), or National Electronic Inquiry Surveillance System (NEISS, supported by Consumer Product Safety Commission) obtain their data from clinics, hospitals, and medical examiners. The deaths or emergencies related to the use of these substances are so few that a 2-fold increase (or decrease) in use could occur without being noted in these figures. Thus DAWN reports did not alert us to the increasing use of paint spray which may presently be the most popular inhalant.

The low incidence of problems associated with inhalant abuse is exemplified by the report of only five deaths associated with N_2O (compared to 28 for carbon monoxide and cyanide) from June 1977 to July 1978 in the Nationwide DAWN system. In one Texas county, four deaths were reported from N_2O use during a similar period.[1] Thus, for most inhalants an unusual incidence in one geographic area may suggest a nationwide trend that is not real. For specific inhalants, we therefore are often limited to the information provided us in reports on very select populations such as reported elsewhere in this issue.[2]

The National Institute on Drug Abuse conducts a household "National Survey on Drug Abuse"[3] which includes all volatile substances under the category of inhalants. Of the 12- to 17-year-olds queried, 1.5% had used one or more substances in the past year and 0.7% had used them in the past month. Lower use was reported for adult populations. Although this does not approach the level of use of alcohol, tobacco, or marihuana, it is comparable to the reported use of either sedatives, cocaine, stimulants, or hallucinogens. Those who are current users (used inhalants in the last month) could exceed one-quarter million American youths under age 18. We expect to have more information on the use of selected inhalants in the 1979 report. However, some anesthetics as well as other substances will still be grouped in a few selected categories.

Most abuses of volatile substances have been called to the public's attention by the press and medical journals. Although ether "jags" and N_2O parties were noted in the 19th century, more recently "glue sniffing" among youngsters was reported in the 1950s, fluorocarbon aerosols in the 1960s and paint sprays in the 1970s. Gasoline sniffing has always been a problem but little noted except on the Indian reservations while paint thinner has been a popular substance used in Mexico.[4]

An analysis of a recent population of 600 youths in a Texas clinic has enabled us to get some perspective of the current use of different volatile substances.[5] From an analysis of the "density of the drug use" in this population, spray paint appeared to be the most popular, closely followed by gasoline and glues. Of the inhalant user groups, over 50% reported use in excess of 100 times. Although this is a biased sample and may not be totally representative of other parts of the U. S., there are other studies and information that generally support much of this study as being representative of inhalant use in general. This study[5] did not indicate a high use of anesthetics as compared to other inhalants by the general population, probably due to the inaccessibility of these substances. However, the high use of N_2O reported within the medical profession may be indicative of its potential abuse by the public at large if this substance were to become more readily available.

As many have noted, the availability of N_2O in pressurized whipped cream cans and "whippets" has made it readily accessible to the general population. More widespread use may occur regardless of whether N_2O is used to replace fluorocarbons in aerosols. Even now there are indications of the widespread use of nitrous oxide on college campuses and substantial use has also been noted in the armed services. A more definitive study of the use of nitrous oxide by select groups may give us a better perspective of the problem in these specific "communities."

The misuse of commercial products has been dramatized by one recent report describing a subject with incoordination and numbness and weakness of limbs.[6] Other reports on neuropathies produced by excessive N_2O use support the rationale linking chronic N_2O use with these disabilities and other toxicities.[7,8] Although deaths associated with anoxia are well known, these neuropathies were somewhat unexpected. However, since knowledge on the subchronic and chronic administration of N_2O and other anesthetics is very limited, we can anticipate seeing other "unexpected" results.

As nitrous oxide is widely used, some efforts have been made to examine the effects following prolonged administration of N_2O. Thus the knowledge that N_2O reacts in vitro with vitamin B_{12} analogs to change their oxidative state has been recently utilized to measure in vivo N_2O effects.[9] These studies partly explain some types of megaloblastic changes. Also, knowledge of these studies has led one investigator to conclude that N_2O reactions with vitamin B_{12} systems may be able to explain the occurrence of associated neuropathies.[10]

There have been some other interesting studies bearing on the mechanism of N_2O action. Although some investigators[11] have noted that the narcotic antagonist, naloxone, reduces the analgesic action of N_2O, the interpretation that this may reduce the anesthetic potency of N_2O has been refuted by several investigators.[12] Whatever the mechanism is and what role N_2O plays in the development of neuropathies and other toxicities will be revealed only by further investigations.

Nitrous oxide is only one of many inhalants abused. The National Institute on Drug Abuse has supported studies to increase our general knowledge on the effects of many types of inhalants. Studies of inhalant abuser populations from psychiatric emergency room and other clinics indicate that these subjects have definite cognitive deficits.[13] From the consistancy of the reports, it would seem that these are not the results of conditions prior to or independent of inhalant use. There is, however, insufficient evidence to determine which substances or conditions of or resulting from abuse are most important in producing toxic effects. It is certain that malnutrition and disease cannot be ignored.

To answer many of these questions, studies are needed to determine the toxic effects produced from acute, 1- to 5-day subchronic or chronic exposure. Due to ethical considerations, conditions are not usually appropriate for exposing humans to most inhalants. However, when repeated exposure is warranted and justified, such as in certain treatments or surgical operations, it would be desirable to take appropriate measures (dose, time of exposure, effects etc.) on these subjects to see whether any long term and/or subtle changes do occur. Studies being conducted to evaluate those concentrations that affect performance of operating room or other personnel may be appropriate.[14]

One study approached the subchronic effects of N_2O by measuring lysosomal damage that occurred in rat lung epithelial cells following nitrous oxide administration over several days.[15] This change may indicate an irreversible or a small but reversible change. One may ask if this condition is related to the anesthetized state in general or to a specific toxic manifestation of N_2O. Hopefully additional studies that are more critically designed to enhance our understanding of long-term exposure to anesthetic agents will be conducted.

Another factor to be considered is the developmental effects of these substances. A recent study demonstrates the sensitivity of the fetus to anesthetics.[16] This may not have been viewed as a severe problem in the past since fewer females were inhalant abusers. However, recent studies that indicate the increase in recreational use of inhalants by young females and the adverse effects of exposure conditions in operating rooms support the need for more studies in this area. In addition, one cannot ignore the potential carcinogenic effects. Although a recent study did not demonstrate any neoplastic effects of several anesthetics,[17] epidemiologic data and other reports on the anesthetic trichloroethylene have raised questions about its being carcinogenic.

There is sufficient need to pursue knowledge regarding the repeated use of these volatile agents. There will undoubtedly be more rather than fewer agents inhaled repeatedly for hedonistic purposes. Those working with humans can provide much needed vital information on the effects of repeated administration; those using animals can probe deeper into the mechanisms of action.

Research in this area demands a strong interdisciplinary approach. To augment these interactions, the anesthetic community has the necessary expertise to assist those in the field of drug abuse to resolve the many questions pertaining to this type of "anesthetization."

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Skeletal Muscle Mitochondria in Porcine Malignant Hyperthermia: Respiratory Activity, Calcium Functions, and Depression by Halothane

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GRONERT, G. A., AND HEFFRON, J. J. A.: Skeletal muscle mitochondria in porcine malignant hyperthermia: respiratory activity, calcium functions, and depression by halothane. Anesth Analg 58:76-81, 1979.

To examine mitochondrial function in malignant hyperthermia, calcium binding and respiratory functions were measured at 37 C in the absence and presence of halothane in mitochondria isolated from the semitendinous muscle of normal and genetically susceptible swine. Oxygen consumption stimulated by a phosphate acceptor, i.e. adenosine diphosphate (ADP), is state 3 respiration; state 4 respiration is that in the absence of ADP. Values for rate of calcium binding and state 3 respiration in susceptible swine were 40 to 60% of those of normal swine. Halothane altered mitochondrial functions in both normal and susceptible swine to a similar degree: with glutamate-malate substrate, halothane markedly inhibited state 3 respiration, had no significant effect on state 4 respiration, and slightly but significantly inhibited the rate of calcium binding. With succinate substrate, halothane slightly inhibited state 3 respiration, slightly stimulated state 4 respiration, and did not alter calcium binding rate. Oxidation of glutamate-malate provides electrons earlier in the cytochrome chain than does oxidation of succinate. The inhibition by halothane of respiration supported by glutamate-malate that was not seen on respiration supported by succinate suggests a mechanism involving the initial energy reactions in electron transfer. Halothane did not release calcium from actively loaded mitochondria. Dinitrophenol uncoupled state 3 respiratory rates similarly, showing that the lower rate in susceptible swine was not due to a limited capacity of the phosphorylating system. The authors conclude that the reduced respiratory and calcium binding activities in mitochondria from susceptible swine support the diagnosis of a myopathy, but that these do not account for the functional and biochemical derangement observed in clinical malignant hyperthermia.

Key Words: HYPERTHERMIA: malignant; METABOLISM: malignant hyperthermia.

UNCOUPLING of oxidative phosphorylation has been hypothesized[1] and discounted[2] as a cause of malignant hyperthermia (MH). However, studies of skeletal muscle mitochondrial functions—calcium binding and release, respiratory activity, and the effects of halothane—have yielded contradictory results[3-8] and consequently have not elucidated the role of mitochondria in MH. Some investigators have

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found reduced respiratory activity,[3, 7] others found no change,[4–6] still others found increased activity[8] Britt reported a decreased capacity for calcium binding that was unaltered by halothane.[8]

Some of these conflicting results may be due to varying experimental conditions such as species, temperature (37 C vs 25 C), anesthetic concentrations, or the use of appropriate control subjects. None of the above authors reported measurements of halothane concentrations in the liquid media of their mitochondrial preparations. The present study was conducted on muscle mitochondria from littermate susceptible and normal Poland China swine at 37 C and includes measured concentrations of halothane in the incubation media. Either glutamate-malate or succinate was used as substrate for mitochondrial metabolism. Oxidation of glutamate-malate provides electrons earlier in the cytochrome chain than does oxidation of succinate, enabling evaluation for specific sites of inhibition.

Materials and Methods

Five genetically susceptible (MH swine) and five littermate normal 20- to 50-kg Poland China swine were given intravenous atropine, 0.4 mg, and thiopental, 10 to 15 mg/kg. They were ventilated so as to maintain an arterial carbon dioxide tension of 40 ± 5 torr, with a Harvard pump through an endotracheal tube using a mixture of 50% nitrous oxide-oxygen. The semitendinous muscle was exposed and 30 to 40 g were removed from its posterior surface and placed in ice-cold 0.15 M sodium chloride. After excision of the muscle, susceptibility or resistance to MH was confirmed from changes in arterial pH, carbon dioxide and lactate in each animal using the dual triggers succinylcholine and halothane.[9] Mitochondria for calcium binding and oxidative phosphorylation studies were isolated according to the method of Dow[10] and all measurements were performed within 4 hours of isolation. The isolation medium consisted of 0.25 M sucrose, 10 mM ethylenediaminetetraacetic acid (EDTA), 50,000 U of sodium heparin per liter, and 25 mM Tris-HCl, pH 7.5. Mitochondria were isolated from the supernatant following centrifugation to remove myofibrils. The mitochondria were then washed and resuspended in 0.4 ml of 0.25 M sucrose per gram of muscle. All procedures were carried out at 0–2 C and the mitochondrial suspensions were stored at 0 C. Mitchondrial protein was measured with the Folin phenol reagent after solubilization of the protein in 0.4 N NaOH.[11]

Calcium binding rate and capacity of mitochondria were measured at 37 C by the Millipore filtration technique[12] in a medium containing 100 mM KCl, 5 mM $MgCl_2$, 20 mM imidazole buffer (pH 6.9 at 37 C), 5 mM adenosine triphosphate (ATP), 5 mM glutamate plus malate or succinate plus 1.5 µM rotenone, 10 to 200 µM $CaCl_2$ with 0.5 µCi of $^{45}CaCl_2$. The reaction was started by adding 0.1 to 0.2 mg of mitochondrial protein per milliliter and was stopped at ½, 1, 2, 5, 10, and 15 minutes by removal of the mitochondria with 0.45-µm diameter Millipore filters. Blanks which lacked substrate were filtered simultaneously. Calcium binding was determined by subtracting the amount of radioactivity in the filtrate of the sample from that of the blank. Calcium binding rate refers to the rate obtained after ½ minute of binding reaction. Calcium binding capacity was read from the plateau of the binding versus time curve, which reached a plateau after 10 to 15 minutes of incubation. The maximal velocity and the Michaelis constant refer to the maximal rate of calcium binding and the calcium concentration at which the half-maximal rate occurs, respectively. Radioactivity was determined by a Packard Tri-Carb liquid scintillation counter.

Mitochondrial respiration was measured polarographically using a Gilson Oxygraph. Oxygen uptake measurements were performed at 37 C in a final volume of 1.5 ml. Oxidation of glutamate plus malate or succinate was measured in the following medium: 0.13% bovine serum albumin, 0.015 M KCl, 0.03 M KH_2PO_4, 5 mM $MgCl_2$, 7 mM EDTA, 0.045 M sucrose, 0.070 M mannitol, 20 mM glucose, and 25 mM Tris-HCl, pH 7.25, 37 C. State 3 respiratory rates were determined after addition of 0.2 µM adenosine diphosphate (ADP) to the reaction medium. State 4 respiratory rate was determined after the added ADP was consumed. ADP stock solutions were standardized by an enzymatic method.[13] Oxygen solubility in the medium at 37 C was taken as 0.39 µg-atoms/ml.[10] State 3 respiratory rate is the rate of respiration in the presence of ADP, state 4 is that obtained after the ADP is expended, and Respiratory Control Index (RCI) is the ratio of state 3 to state 4.

Noncollagenous protein of the muscle biopsies was determined as follows: 100-mg samples were dispersed in 15 ml of 0.05 N NaOH with the Polytron homogenizer. After solubilization of protein for 18 hours the solution was centrifuged and the protein content of the supernatant determined with the Folin phenol reagent.[11] There was no difference in noncollagenous protein content of the muscles of normal, 195.7 ± 10.8 mg of protein/gram of muscle wet weight, and MH swine, 206.4 ± 15.6 mg/g. The permeability of both types of mitochondria was assessed by measuring the capacity to oxidize reduced nicotine adenine dinucleotide (NADH) added to the reaction medium. The uncoupling effect of 0.13 to 0.20 mM dinitrophenol on state 3 respiration was determined in both normal and MH mitochondria.

Halothane was delivered from a calibrated vaporizer to give concentrations in the 0.5–6% range in the media used for measurement of calcium binding or oxidative phosphorylation. Pilot studies showed that halothane equilibration was complete in 10 minutes when the halothane-oxygen mixture was pumped at a constant rate (600 ml/min) through a sintered glass disc into the appropriate medium, similar to the method previously described by Muldoon et al.[14] Calcium binding studies were performed in 25-ml Erlenmeyer flasks equilibrated for 10 minutes with halothane. Mitochondria were added to the medium after removal of the sintered glass disc and the same halothane concentration was blown over the surface of the medium at the flow rate of 600 ml/min. After a further 5 minutes of equilibration the binding reaction was started by adding substrate. Samples were removed by pipette for filtration and radioactive counting at various times. Halothane was discontinued during the course of the reaction only during pipette sampling (less than 10 seconds/pipetting). For mitochondrial respiratory studies, halothane-equilibrated medium was transferred to the oxygraph reaction vessel with a Hamilton gas-tight syringe, and the mitochondria were equilibrated with halothane in the medium for 5 minutes before initiating state 3 respiration with ADP. The concentration of halothane in reaction medium was determined in every experiment.[15]

Significance of differences between the two groups of swine was determined by Student's unpaired t-test, intragroup analysis by paired t-test, $p < 0.05$ considered significant.

Results

The rate of mitochondrial calcium binding with glutamate-malate substrate was 2½-fold greater in normal than in MH mitochondria and this difference was evident at all calcium concentrations examined (Fig 1). When these data are plotted by the direct linear method of Cornish-Bowden,[16] the normal and MH mitochondria exhibited similar Michaelis constant values of about 30 μM calcium and the maximal velocity was reached at about 200 μM calcium. However, the maximal velocity of calcium binding by the normal mitochondria was approximately 400 nmol/mg/min compared with a corresponding value of about 100 nmol/mg/min by the MH mitochondria. The calcium binding capacity of the MH mitochondria was significantly lower than that of the normal mitochondria (Table 1).

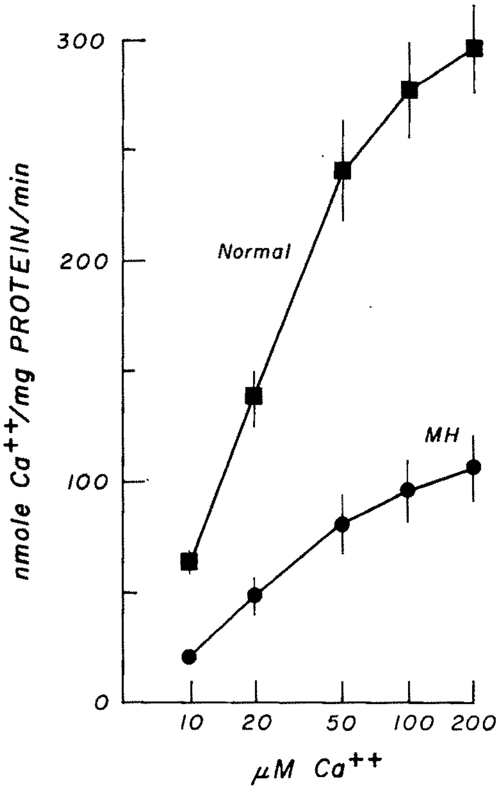

FIG 1. Rate of mitochondrial calcium binding as a function of the log of the calcium ion concentration at 37 C with a glutamate-malate substrate (mean ± SE, n = 5); normal: mitochondria isolated from skeletal muscle of normal swine; MH: mitochondria from susceptible swine.

The rate of mitochondrial calcium binding with succinate substrate (Fig 2) was likewise 2½-fold greater in normal than in MH mitochondria. Halothane (Fig 2) depressed mitochondrial calcium binding rate in the presence of glutamate-malate but had minimal effect on mitochondrial calcium binding rate in the presence of succinate. The binding capacities of normal and MH mitochondria were minimally depressed by concentrations of halothane up to 4%, using either glutamate-malate or succinate as substrates. Halothane up to 4% did not cause release of calcium from actively loaded mitochondria even after 15 minutes of exposure at 37 C.

State 3 respiratory rate was significantly higher in normal than in MH mitochondria in the presence of either glutamate-malate or succinate substrates (Fig 3). However, halothane inhibited glutamate-malate state 3 respiration more than succinate state 3 respi-

TABLE 1
Mitochondrial Binding Capacity (Nanomoles of Ca^{2+} per Milligram of Protein) at 37 C with Glutamate-Malate Substrate (Mean ± SE)*

	Calcium concentration (μM)				
	10	20	50	100	200
MH	72.3 ± 10.7	179 ± 19	276 ± 41	326 ± 45	360 ± 43
Normal	222 ± 21	376 ± 34	463 ± 33	510 ± 30	556 ± 39

* MH different from normal at all calcium concentrations, $p < 0.05$.

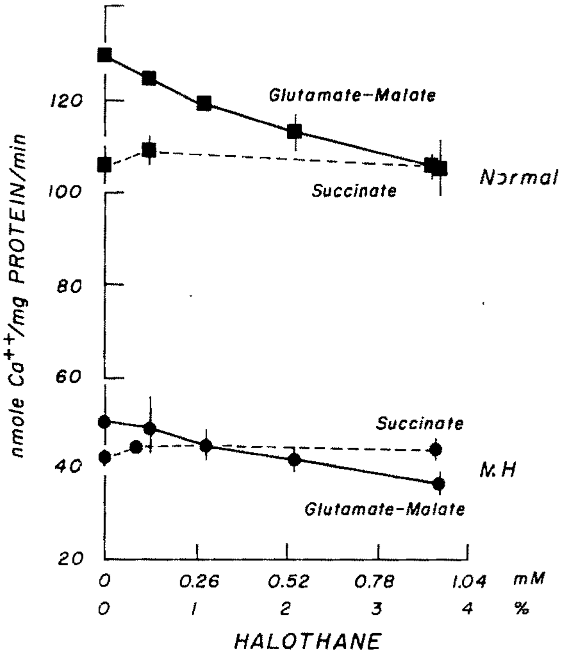

FIG. 2. Rate of mitochondrial calcium binding at 20 μM calcium as affected by halothane at 37 C with succinate and glutamate-malate as substrates (mean ± SE, n = 3); normal: mitochondria isolated from skeletal muscle of normal swine; MH: mitochondria from susceptible swine.

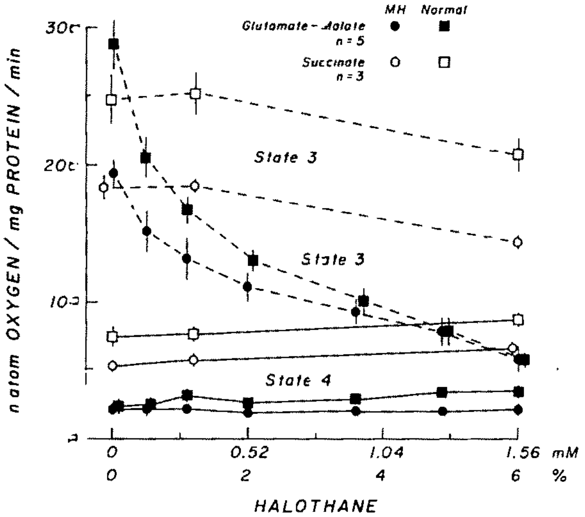

FIG. 3. State 3 (- - -) and state 4 (——) mitochondrial respiration as a function of halothane concentration at 37 C using succinate or glutamate-malate substrate (mean ± SE); normal: mitochondria isolated from skeletal muscle of normal swine; MH: mitochondria from susceptible swine.

ration in mitochondria obtained from both normal and MH swine (Fig 3). State 4 respiratory rates were similar in normal and MH mitochondria when glutamate-malate was the substrate. However, with succinate as the substrate, MH state 4 respiratory rate, 54 ± 3 nano-atoms of oxygen/milligram of protein/minute, was significantly less than that observed in normal mitochondria, 76 ± 5 (Fig 3). State 4 respiration was slightly stimulated by halothane concentrations in excess of 3.7% in the normal mitochondria using both substrates and in the MH mitochondria using succinate as substrate. The RCI of MH mitochondria in the absence of halothane (Table 2) tended to be lower than that of normal mitochondria using glutamate-malate substrate although the difference was not significant ($p = 0.06$); the RCI, 3.4, was similar in both using succinate substrate. Due to the more marked effect of halothane on state 3 respiration, RCI was reduced to values between 1 and 3. The efficiency of oxidative phosphorylation (P/O) was the same in MH and normal mitochondria. With glutamate-malate substrate, it was about 2.9, with succinate about 1.9. Halothane tended to decrease P/O ratios (by about 0.[illegible] to 0.3) of both mitochondrial types with either substrate.

The permeability of mitochondria from MH and normal swine was similar, in that both exhibited slow and similar rates of oxidation of exogenous NADH, and halothane inhibited oxidation to the same extent in each. Dinitrophenol uncoupled state 3 respiration to the same extent in both normal and MH mitochondria. Concentrations of halothane in liquid media were 0.132 ± 0.005 mM, 0.51%; 0.282 ± 0.009 mM, 1.1 %; 0.542 ± 0.013 mM, 2.1%; 0.957 ± 0.009 mM, 3.7%; 1.280 ± 0.026 mM, 4.9%; 1.554 ± 0.044 mM 6.0%.

Discussion

Both respiratory activity and the rate and capacity of calcium binding were significantly lower in mito-

TABLE 2
Effect of Halothane on Respiratory Control Index (Mean ± SE)*

Glutamate-Malate		Succinate		% Halothane
MH	Normal	MH	Normal	
9.4 ± 1.1†	14.2 ± 1.8†	3.4 ± 0.1	3.4 ± 0.1	0
7.4 ± 0.7	9.6 ± 1.6			0.5
6.0 ± 0.5‡	6.1 ± 1.3‡	3.2 ± 0.2§	3.3 ± 0.1§	1.1
5.8 ± 0.5‡	5.6 ± 0.9‡			2.1
4.9 ± 0.6‡	3.9 ± 0.6‡			3.7
4.1 ± 0.8‡	2.4 ± 0.3‡			4.9
2.8 ± 0.6‡	1.8 ± 0.3‡	2.1 ± 0.1§	2.4 ± 0.1§	6.0

* Respiratory control index = ratio of state 3 oxygen consumption to state 4 oxygen consumption. MH, mitochondria from skeletal muscle of susceptible swine; n = 5 except § which indicates n = 3.

† Difference between MH and normal, $p = 0.06$.

‡ Different from 0% halothane, $p < 0.05$.

chondria obtained from MH swine than in those obtained from normal swine. This suggests that an energy-linked function of mitochondria such as active calcium transport is considerably less in MH animals, and that MH mitochondria may have an impaired divalent cation transport system. Halothane had similar effects in both normal and MH mitochondria, with minor inhibition of the rate of calcium binding and pronounced inhibition of respiratory activity. Mitochondria calcium binding capacity was not altered by halothane.

The physiologic role of mitochondrial calcium transport in skeletal muscle remains speculative even though this function is a common property of mitochondria of tissues as diverse as liver and brain.[17] It is presently believed that the sarcoplasmic reticulum is the primary calcium accumulating organelle in skeletal muscle fibers, and that mitochondria may play a reserve role in removing sarcoplasmic calcium.[17,18] This is because the maximal rate of calcium binding by mitochondria occurs at higher calcium concentrations than does the maximal rate of calcium binding by sarcoplasmic reticulum. Since MH mitochondria have only one-third the normal ability to transport calcium, their role in calcium homeostasis would be limited, suggesting that the sarcoplasmic reticulum might have to cope with excess calcium during a crisis.

The rate of respiration during active phosphorylation of ADP can be considered to be a quantitative measure of the ability of mitochondria to produce ATP. The state 3 respiratory rate represents the maximal rate of substrate oxidation available for maximal rate of ATP production from ADP and inorganic phosphate. The reduced rate in MH mitochondria may be a limiting factor in energy production under circumstances where demand for ATP is high, e.g. severe muscular activity, physical stress. The MH mitochondria tended to be less "tightly coupled" than normal mitochondria, suggesting that the physiologic control of the rate of respiration by phosphate acceptor may be slightly diminished in MH. There were, however, no differences in P/O ratios, showing that the phosphorylating capacity of mitochondria is intact. The fact that dinitrophenol produced the same degree of uncoupling of state 3 respiration in normal and MH mitochondria indicates that the decreased state 3 respiratory rate in MH mitochondria is due to decreased electron transferring capacity of the respiratory chain rather than to decreased capacity of the phosphorylating system. Because these mitochondria already have a reduced respiratory capacity, the cellular consequences of halothane inhibition of state 3 respiration would be greater in MH animals, and may bear some relationship to the unexpectedly small increase in whole body oxygen consumption observed during active MH.[9] The lower rate of ATP production by oxidative metabolism would have to be compensated by an appropriate increase in glycolysis in order to meet the requirements of muscular activity and to maintain a normal energy charge.

Data on skeletal muscle mitochondrial function by other investigators are difficult to compare because of differences in technique: Berman and Kench,[3] Britt et al,[8] Denborough et al,[5] and Eikelenboom and van den Bergh[7] studied pigs; Britt et al[4,6] also studied humans. Presumably all their studies were at 25 C, although this is specified only on three occasions.[4,6,7] None reported halothane concentrations in liquid media. Whereas Britt et al also reported normal human values[4,6] and Eikelenboom and van den Bergh[7] used abattoir muscle pH values to determine normal and susceptible swine, the remaining porcine studies either did not mention values from normal swine,[3] did not identify screening methods used to distinguish normal from susceptible,[5,8] or compared values from unrelated swine.[8]

In humans, Britt et al[4,6] found no differences between normal and MH subjects in regard to respiratory functions, and halothane decreased state 3 respiration similarly in both. In contrast, Britt et al[8] reported increased respiratory function in mitochondria from MH pigs and decreased capacity for calcium uptake. Denborough et al[5] found no differences in respiratory function in normal and MH Landrace pigs, but, as compared to unrelated pigs, exaggerated responses to halothane. Our results are similar to those of Berman and Kench[3] and Eikelenboom and van den Bergh.[7] In general, all investigators noted depressant effects of halothane upon respiratory function—inhibition of NAD-dependent substrate oxidation and a slight uncoupling of oxidative phosphorylation that was similar in normal and MH mitochondria This effect of halothane is also similar to that originally demonstrated in liver mitochondria by Cohen and Marshall.[19]

The reduced respiratory and calcium binding activities of MH mitochondria do not explain the initial functional and metabolic derangements observed in MH but they do offer evidence that porcine MH is a myopathic condition. Reduced mitochondrial respiratory activity is a feature of muscular dystrophy[20] and of experimental dystrophy such as that due to vitamine E.[21] Also, abnormal mitochondria have been previously observed in ultastructural examination of human MH muscle.[22, 23] Since the clinical symptoms of these myopathies cannot be correlated with the biochemical defects, it is probable that the mitochondrial alterations are nonspecific manifestations of the disease process. It is possible that the mitochondrial changes observed here in MH swine may also be associated with changes consequent to some as yet unknown primary lesion.

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ANESTH ANALG
58:82-84, 1979

Serum Cholinesterase Levels in Patients with Cancer

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KANIARIS, P., FASSOULAKI, A., LIARMAKOPOULOU, K., AND DERMITZAKIS, E.: Serum cholinesterase levels in patients with cancer. Anesth Analg 58:82-84, 1979

Serum cholinesterase levels were determined in 180 patients with carcinoma and in 146 normal subjects. Serum cholinesterase activity was significantly lower in patients suffering from cancer than in normal controls, though still within the normal range. The degree of depression of serum cholinesterase activity was influenced by the extent to which the malignancy had spread and by the site of the primary lesion.

Key Words: ENZYMES: cholinesterase; CANCER: serum cholinesterase.

ALTHOUGH no known physiologic function has been found for serum cholinesterase, the enzyme is of theoretical and practical interest for the anesthetist since it inactivates drugs used in anesthesia, especially succinylcholine and ester-type local anesthetics such as procaine and 2-chloroprocaine. Low serum cholinesterase levels have been reported in patients with cancer.[1] However, there are no available data to indicate whether the site of origin of tumors and the degree of their spread are correlated with levels of serum cholinesterase. The present study was designed to obtain such data.

Materials and Methods

Patients

Serum cholinesterase levels were determined in 180 patients suffering from histologically proven cancer and in 146 healthy subjects (blood donors) used as controls. Patients with hepatic disease other than that related to the tumor involvement, with hypertension, or with other major concurrent disease were excluded, as were pregnant patients. Studies were not performed during the course of radiotherapy or chemotherapy or during administration of drugs known to depress serum cholinesterase in vivo.

Patients were classified according to the degree of spread of their tumor: group I-local carcinoma, no evidence of spread of tumor beyond the organ of origin; group II-nonhepatic metastases with evidence of extension of the tumor beyond the organ of origin but without evidence of liver involvement; group III-hepatic metastases, hepatic involvement by the tumor cells (by direct extension or by metastases).

Of the 180 patients with carcinoma (84 men and 96 women), 62 patients had breast cancer, 32 had cancer of the genitourinary tract, 45 patients had cancer of the gastrointestinal tract, 14 had lung cancer, and in 27 patients the primary lesions were on the lips, skin, and soft tissues. The average age was 61 years. None of the 146 control subjects (71 men and 75 women had a history of liver disease, and liver function tests were within normal limits. The average age of the control patients was 51 years.

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Blood Samples

Preprandial 2.5-ml samples of venous blood were selected at 7:30 a.m. The blood was centrifuged at 2,000 rpm and cholinesterase levels were determined in the extracted serum. Centrifugation and enzyme measurements were performed within 1 hour after the samples were obtained.

Assay Method

Serum cholinesterase levels were determined by means of a colorimetric assay technique at 25 °C and pH 7.7[2] (Boehringer cholinesterase test kit, normal values 3,000 to 9,300 units/L). Butyrylthiocholine was the substrate and the thiocholine produced by its enzymatic hydrolysis reacted with 5,5-dithiobisnitrobenzoate to form 2-nitromercaptobenzoate which was estimated photometrically at a wavelength of 405 nm (Coleman Junior II Photometer, cuvette Icm light path). Replicate determinations were performed in all samples; there was no significant difference between the two determinations. Results are given as the means of the two replicate determinations. Dibucaine numbers were also determined in all samples by the method of Kalow and Genest.[3]

Results

Serum cholinesterase values in the 180 patients with carcinoma, though still within normal limits, were significantly lower than they were in the control subjects (Table 1). Of the 180 patients studied, 120 had local carcinoma, 38 had nonhepatic metastases, and 40 had hepatic metastases or direct extension to the liver. The mean serum cholinesterase values in patients with hepatic metastases (group III) were significantly lower than they were in patients with local carcinoma (group I) or in patients with nonhepatic metastases (group II) (Table 2). Low serum cholinesterase levels were found in 26.4% of the patients in group I, in 39.4% of the patients in group II, and in 67.5% of the patients in group III.

TABLE 1

Mean Serum Cholinesterase Values in Patients with Cancer and in Normal Healthy Controls*

Group	No. of cases	Mean ± SE serum cholinesterase levels
		units/L
Patients with cancer	180	3427 ± 93.2
Controls	146	4850 ± 93.2

* $p < 0.01$.

TABLE 2

Percentage of Patients with Low Serum Cholinesterase and Mean Serum Cholinesterase Values According to the Spread of Carcinoma*

Group	Cases with serum cholinesterase <3000 units/L	Mean ± SE serum cholinesterase levels
	%	*units/L*
I Local carcinoma	26.4	3723.75 ± 113.3
II Nonhepatic metastases	39.4	3446.27 ± 207.2
III Hepatic metastases	67.5	2578.00 ± 150.1

* $p < 0.01$ between I and III; $p < 0.01$ between II and III.

TABLE 3

Site of Primary Lesion and Serum Cholinesterase Levels*

Site of origin	Cases with serum cholinesterase <3000 units/L	Mean ± SE
	%	
Breast	19.4	3942.50 ± 139.2
Miscellaneous†	22.2	3757.00 ± 274.0
Genitourinary tract	44.4	3241.68 ± 182.6
Gastrointestinal tract	56.3	2940.80 ± 194.9
Lung	78.0	2178.60 ± 210.7

* $p > 0.25$ between I and II (NS (no statistically significant difference)); $p < 0.025$ between I and III (SS (statistically significant difference)); $p < 0.0005$ between I and IV (SS); $p < 0.0005$ between I and V (SS); $p > 0.10$ between II and III (NS); $p < 0.01$ between II and IV (SS); $p < 0.0005$ between II and V (SS); $p > 0.10$ between III and IV (NS); $p < 0.0005$ between III and V (SS); $p < 0.01$ between IV and V (SS).

† Miscellaneous group includes primary lesions of the lips, skin and soft tissues.

The site of primary lesion also influenced serum cholinesterase values (Table 3). Carcinoma of the lung (bronchogenic carcinoma) was associated with a mean value of 2,178.6 units/L of serum cholinesterase which was significantly lower than the mean values associated with other types of carcinoma. Only 19.4% of the patients with mammary carcinoma had enzyme levels less than 3,000 units/L compared to 79% of those with lung carcinoma, 44.4% of those with genitourinary carcinoma, and 56% of those with gastrointestinal tumors.

All patients and all control subjects had dibucaine numbers consistent with typical cholinesterase enzyme.

Discussion

Serum cholinesterase levels may be low in patients in nutritional deficiency states and in women during normal pregnancy. In fulminant hepatic failure serum cholinesterase concentrations are, however, usually within normal limits.[4] Enzyme activity is depressed by many cholinesterase inhibitors including not only therapeutic agents such as echothiophate eye drops, tacrine, hexafluorenium but also organosphosphate poisons. Some anticancer agents,[5] as well as pancuronium and ketamin,[6-8] may also temporarily decrease serum cholinesterase activity.

Mean serum cholinesterase values were lower in our patients with cancer than they were in control subjects but were still within the lower normal range. Decreases in cholinesterase levels were more evident in patients with metastases. The fact that patients with hepatic metastases had significantly low serum cholinesterase values is, we believe, not attributable to reduction in enzyme synthesis. All patients, even those with liver involvement confirmed by explorative laparatomy or liver biopsy, had normal liver function tests.

Serum cholinesterase levels were also related to the anatomic site of the primary lesion. Certain tumors (breast, miscellaneous) appeared to have less effect on enzyme levels than did other tumors (lung, gastrointestinal tract, and genitourinary tract). Most conspicuous was the significiantly lower levels of serum cholinesterase associated with carcinoma of the lungs (Table 3). This suggests that certain types of carcinoma may produce an inhibitor of serum cholinesterase.

The significance of lower levels of serum cholinesterase observed in patients with carcinoma lies in possible prolongation of paralysis following administration of succinylcholine. We found in unpublished studies that in patients with serum cholinesterase levels of 2,000 units/L or less, succinylcholine (50 mg) wore off after 12 to 15 minutes. In patients with serum cholinesterase values of about 5,000 units/L recovery following 75 mg of succinylcholine occurred within approximately 4 minutes.

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Nebulized Racemic Epinephrine by IPPB for the Treatment of Croup

Racemic epinephrine has been advocated for the treatment of croup, but controlled studies have not proved it more effective than saline. Twenty patients (aged 4 months to 5 years) hospitalized with acute croup and persistent inspiratory stridor at rest were randomly assigned to one of two treatment groups: saline or racemic epinephrine, both nebulized and delivered by intermittent positive pressure breathing. Clinical scores were significantly improved ($p < 0.01$) at 10 and 30 minutes following the treatment with racemic epinephrine but not at 120 minutes. Racemic epinephrine was significantly more effective than saline at 10 ($p < 0.01$) and 30 minutes ($p < 0.05$) but not at 120 minutes after the treatment. Nebulized racemic epinephrine is an effective treatment for the acute signs of croup. *(Westley CR, Cotton EK, Brooks JG: Nebulized racemic epinephrine by IPPB for the treatment of croup. Am J Dis Child 132:484-487, 1978)*

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Analgesic Properties of Lidocaine in Mice

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MOORE, P. A., AND BURNEY, R. G.: Analgesic properties of lidocaine in mice. Anesth Analg 58: 85–87, 1979.

The analgesic properties of lidocaine and morphine were compared in mice using a hot plate stimulus. An analgesic response was defined as an increase in the time required for an animal to attempt to escape by jumping. When compared to saline-treated controls, lidocaine produced a statistically significant dose-related delay in response to heat. Dose-response curves for morphine and lidocaine indicated that morphine has greater potency and efficacy. Naloxone (1.0 mg/kg) reversed the analgesic response due to morphine (10 mg/kg) but had no effect on the analgesia produced by lidocaine (50 mg/kg).

Key Words: ANESTHETICS, Local: lidocaine; ANTAGONISTS, Narcotic: naloxone.

LIDOCAINE has been used for a variety of therapeutic purposes other than local anesthesia. It is commonly used intravenously as an antiarrhythmic agent in the management of acute ventricular arrhythmias. Administered systemically, lidocaine[1,2] as well as procaine[3-5] has been used to produce significant postoperative analgesia in humans.

Lidocaine has also been employed as an adjunct during general anesthesia.[6,7] In animals, lidocaine decreases the MAC of cyclopropane by 42%[8] and the MAC of halothane by 45%.[9] The purpose of this study was to investigate the mechanism of the analgesic effect of systemically administered lidocaine.

Methods and Materials

The hot plate test used in this study was a modification of the test described by Eddy et al.[10] The instrument was a thermostatically controlled metal plate (Technilab Instruments, model 475) equipped with a Plexiglas cylinder (height 32 cm and diameter 16 cm). The temperature was maintained at 55 ± 0.5 C. Reaction times were defined as the time between the animal's initial contact with the plate to the time the animal attempted to escape by jumping. Mice not responding within 100 seconds were removed and a reaction time of 100 seconds was recorded. For simplicity, increased reaction times will be referred to as an analgesic response with the understanding that pain and analgesia cannot be accurately defined in animals. The testing period was limited to 0700 to 0900 hours to minimize circadian variations and animals were exposed to the plate only once during the daily testing period.

Male, Swiss-Webster mice (Flow Laboratories, Dublin, Virginia), weighing 35 to 45 gm each, were acclimated to the animal quarters for 3 weeks before testing. They were housed five to a cage (28 × 16 × 12 cm), were permitted free access to food and water, and were exposed to artificial light from 0600 to 1800 hours. The animals were moved to an adjoining laboratory 1 hour before the experiments. To control the fluctuations in the temperature and noise level during the 2-hour testing period, the control animals were tested alternately with the drug animals.

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All drugs were administered intraperitoneally in a volume of 1 ml/100 gm of body weight. Crystals of lidocaine hydrochloride (Winthrop Laboratories, New York, New York), morphine sulfate (Mallinckrodt, Inc., St. Louis, Missouri), and naloxone hydrochloride (Endo Laboratories, Inc., Garden City, New York) were dissolved in 0.9% NaCl solutions.

Three studies were conducted. The first determined the jump response 5, 15, 30, and 60 minutes after injection of 20, 30, 40, or 50 mg/kg of lidocaine. Each dose-time value is the mean value of 20 animals and was compared to the mean control value of 20 animals given saline using a Student's *t*-test.

The second study determined the effect of naloxone on the jump response following lidocaine (50 mg/kg), morphine (10 mg/kg), or saline treatments. Either naloxone (1 mg/kg) or saline was injected 15 minutes after morphine, lidocaine, or saline; 15 minutes later the animals were tested. A total of 120 animals (20 animals for six conditions) was tested and mean reaction times were determined. A Student's *t*-test determined the significance of differences between animals given naloxone and control groups.

The third study compared lidocaine and morphine dose-response curves by administering 5, 7, 10, and 15 mg/kg of morphine and 20, 30, 40, and 50 mg/kg of lidocaine to 160 animals (20 animals per dose). Since previously determined response-time curves for lidocaine and morphine were reasonably flat between 15 and 45 minutes, testing was done 30 minutes after injection. The percentage of animals that had reaction times greater than twice the control time was calculated for each dose. The statistical analysis used for determining differences in efficacy was a chi square test, and for differences in potency, a linear regression analysis was used.

Results

The analgesic responses to varying doses of lidocaine are shown in Fig 1. Significant responses ($p < 0.01$) were found 15 and 30 minutes after the injection of 40 and 50 mg/kg of lidocaine. The 5-minute response for lidocaine (50 mg/kg) is absent because 15% of the mice in this group convulsed immediately upon contact with the hot plate. This latter dose is reasonably close to the previously reported median convulsant dose (CD_{50}) for mice of 65 mg/kg.[11] The mean reaction time (±SE) for the control animals ($n = 160$) was 30.6 ± 3.2 seconds.

A significant ($p < 0.01$) change in response following naloxone (Fig 2) is seen only for morphine (10 mg/kg). Naloxone had no effect on the response of animals treated with saline or lidocaine (50 mg/kg).

The dose-response relationships for morphine and lidocaine are shown in Fig 3. An analgesic response to lidocaine at doses greater than 50 mg/kg was limited by the onset of convulsions. The maximal response produced by morphine is significantly greater than that produced by lidocaine ($p < 0.01$). A linear regression analysis was utilized to determine the two slopes. Comparison of the standard errors of

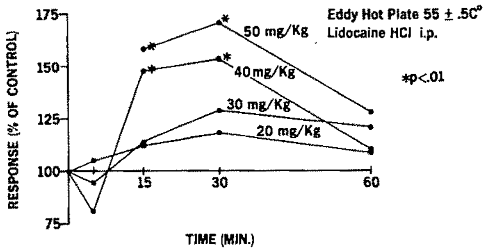

FIG 1. Response-time curves determined 5, 15, 30, and 60 minutes after intraperitoneal lidocaine hydrochloride. Each point represents the mean value of 20 treated mice compared to that of 20 controls.

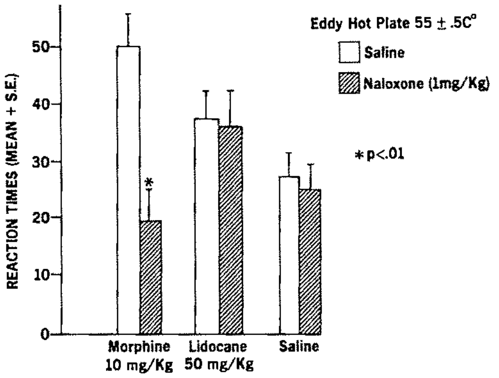

FIG 2. Naloxone interaction with morphine and lidocaine as compared with saline. The response values represent the mean reaction times (+SE) of 20 animals.

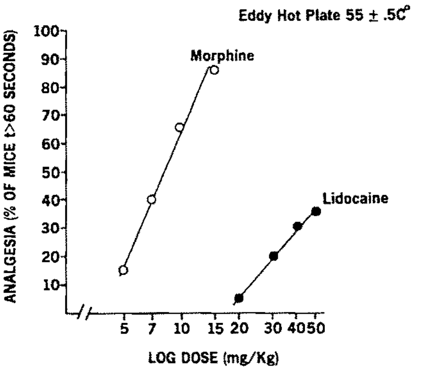

FIG 3. Log dose-response curves for morphine and lidocaine. The analgesic response values represent the percentage of reaction times greater than twice control values.

the regression coefficients revealed that the slopes differed significantly ($p < 0.05$).

Discussion

The time course of the lidocaine response is unusual. During the 5-minute period after injection (Fig 1) lidocaine appeared to have no effect or possibly a negative effect. Whole blood concentrations following intraperitoneal lidocaine, determined previously by one of us (P.A.M.),[12] attain a maximum value of approximately 5 to 6 μg/ml during this initial period. Lidocaine levels 15 and 30 minutes after injection, at a time when analgesia is most profound, have decreased to between 1.0 and 2.0 μg/ml.

This apparent reversal of a dose-dependent response was also reported by a study[8] of the effect of lidocaine on the MAC of cyclopropane in rats. With increasing plasma levels of lidocaine, a plateau effect was demonstrated. The maximum reduction in the MAC of cyclopropane was obtained at 1 μg/ml of plasma lidocaine, while increasing the concentration of lidocaine to 5.5 μg/ml produced no further reduction. This observation as well as ours may reflect CNS depression at lower concentrations and CNS stimulation at higher concentrations of lidocaine.

The analgesic response seen in mice following lidocaine administration does not appear to involve opiate receptors. Naloxone, at a dose which completely reversed the morphine effect, was unable to alter the response to lidocaine, a finding that supports this conclusion. The fact that the dose-response curves for morphine and lidocaine are not parallel (Fig 3) constitutes additional presumptive evidence for different mechanisms of action.[13]

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Hypertension Treatment with Stellate Block

Unilateral stellate ganglion block (right or left) was performed using lidocaine in 27 patients with hypertension early after coronary bypass surgery. The stellate block led to rapid and sustained control of blood pressure in 18 patients (9 of 15 with right stellate block and 9 of 12 with left stellate block) The reduction in arterial pressure was associated with significant ($p < 0.01$) reductions in total peripheral resistance and heart rate but no significant changes in cardiac output or central venous or left atrial pressures. This hemodynamic pattern as well as effectiveness of a unilateral approach suggests that the stellate block reduced arterial pressure by interrupting the afferent limb of a pressor reflex from the heart or great vessels, or both. The procedure was free from side effects and helped avoid prolonged administration of antihypertensive drugs. *(Tarazi RC, Estafanous FG, Fouad FM Unilateral stellate block in the treatment of hypertension after coronary bypass surgery: implications of a new therapeutic approach. Am J Cardiol 42:1013–1018, 1978)*

ANESTH ANALG
58:88-92, 1979

Gastric Excretion of Intravenously Administered Meperidine in Surgical Patients

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TRUDNOWSKI, R. J., AND GESSNER, T.: Gastric excretion of intravenously administered meperidine in surgical patients. Anesth Analg 58:88–92, 1979.

We have demonstrated sequestration of unchanged meperidine in gastric juice of humans following intravenous administration. Concentrations attained were as great as 360 times plasma concentration. The drug was first detected between 5 and 15 minutes after administration. This phenomenon appears to be due to ionization and ion trapping of meperidine in gastric juice.

Key Words: ANALGESICS, Narcotic: meperidine; PHARMACOKINETICS: meperidine; GASTROINTESTINAL TRACT: stomach.

NITROUS oxide-oxygen anesthesia with intravenous meperidine has been used to varying degrees since its introduction by Neff in 1947. In the course of studies on the distribution of meperidine following its intravenous administration, we observed that significant amounts of the drug were sequestered in gastric juice following intravenous administration. A preliminary communication reports this occurrence during the postoperative period in four patients.[1]

We undertook our present study to determine whether significant gastric meperidine accumulation occurs during anesthesia and surgery, and, if so, how soon it appears, the course it follows, and how much might accumulate during surgery and in the early postoperative period.

Methods and Procedures

Patients included in the study were those receiving intravenous meperidine during nitrous oxide-oxygen anesthesia for surgery for malignant tumors or their sequellae. The study was explained to the patients and they consented to be subjects. Preoperative medication consisted of diazepam (5 to 10 mg) and scopolamine (0.4 mg) given intramuscularly. We inserted a Salem nasogastric sump and obtained a gastric juice sample before administration of meperidine. We also obtained a meperidine-free venous blood sample at the time the first intravenous line for medication was inserted. A second intravenous catheter for obtaining later blood samples was placed in the opposite arm. Anesthesia was induced with intravenous injections of meperidine and diazepam. A local anesthetic spray of the mouth, throat, and larynx facilitated endotracheal intubation. After meperidine administration, periodic samples of gastric juice and venous blood for duplicate determinations of pH and meperidine levels were collected. We used a Radiometer microelectrode unit to measure specimen pH. Meperidine concentrations were determined by gas chromatography on a glass column packed with 3% OV-17 on 100- to 200-mesh Gas Chrom Q, using the method of Goehl and Davison,[2] with the following modification: the 0.5- or 1.0-ml biological samples were extracted with 15 ml of benzene after being alkalinized with 2.5 or 2.0 ml of 0.1 N sodium hydroxide, saturated with sodium chloride.

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We divided the study into the following phases:

1. Analysis of gastric samples to determine whether meperidine accumulates in gastric juice during anesthesia and surgery in significant concentrations. This required two samples: a control and one obtained during operation at a random time after meperidine administration.

2. Determination of the earliest time when meperidine appears in stomach contents. Here, we obtained gastric samples (a) before meperidine administration and (b) 1, 2, 3, 4, 5, 10, and 15 minutes after the first administration of intravenous meperidine.

3. Comparison of plasma and gastric levels of meperidine during anesthesia and surgery and for 3 hours in the postoperative period. Gastric samples, in addition to the control, were collected as follows: (a) 5, 10, 15, 30, 45, and 60 minutes after the administration of meperidine required for induction and intubation; (b) every 30 minutes while meperidine was given during surgery; and (c) 5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 minutes after the last dose of meperidine. Plasma samples following the control were collected at the same time as gastric samples in 3a above, and every 60 minutes for the rest of the study.

4. Determination of the total amount of meperidine sequestered in the stomach during the study. We withdrew as much gastric juice as possible during anesthesia and surgery for volume and drug concentration determination. In two patients, gastric volume and drug concentration were also measured postoperatively at 2.5 hours and 2.75 hours, respectively.

Results

Ten women and 10 men between the ages of 31 and 81 years (mean age 50 years, SD 14.07) were studied. A.S.A. physical status ranged from 1 to 3 (mean 2.57, SD 0.57). All except one had surgery for the treatment of malignant tumors or their sequellae.

The pH of the venous blood samples was between 7.30 and 7.33. Most gastric samples had a pH between 1.2 and 1.8. Four patients had one or two early gastric samples with pH between 4.6 and 6.1.

The first phase (Table 1) of the study showed that unchanged meperidine accumulates in gastric juice in concentrations greater than in plasma. Although the concentrations were variable, this positive ratio always occurred. The gastric concentrations could become quite large. Fig 1 shows this in a patient studied in the fourth phase. These meperidine concentrations are the highest we recorded, over 1000 μg/mL after a total dose of 650 mg of meperidine over 4.75 hours.

TABLE
Gastric and Plasma Meperidine Concentrations during Phase 1

Patient	Body fluid*	Meperidine concentration after meperidine administration†
		μg/ml
1	P	1.50 (75 min)
	G	23.80
4	P	0.82 (120 min)
	G	5.54
6	P	2.81 (300 min)
	G	55.60
12	P	0.40 (60 min)
	G	41.00
13	P	2.80 (60 min)
	G	120.00
14	P	3.60 (60 min)
	G	153.80
15	P	1.97 (60 min)
	G	7.77
16	P	1.30 (30 min)
	G	21.14
17	P	1.84 (30 min)
	G	19.01

* P, plasma; G, gastric juice.

† Meperidine concentration before meperidine administration was zero in all patients.

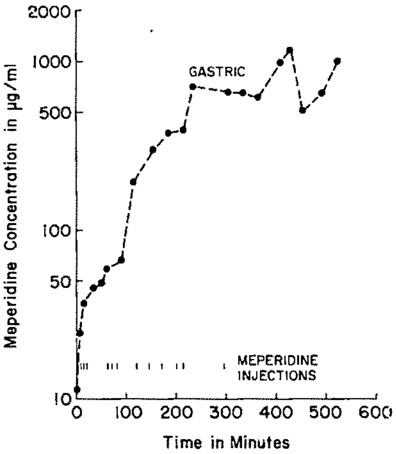

FIG 1. Accumulation of meperidine in gastric juice of patient 8. Vertical bars designate times of meperidine injection in 50-mg increments.

We recovered a total of 23.1 mg of meperidine from this patient's gastric contents during the study.

Table 2 shows the time when meperidine was first detected in gastric contents of patients participating in the second phase of the study. The drug appeared in one patient's gastric fluid at the end of 5 minutes. All patients had detectable amounts at the end of 15 minutes.

Data obtained from patients in the third phase, in which we followed meperidine levels throughout anesthesia, are summarized in Table 3. Gastric levels of drug remained high or even increased in most patients, even though plasma levels fell after the last dose was given. Fig. 2 is an example of this persistently high gastric level. Plasma levels in this patient varied between 1 and slightly over 3 µg/ml, falling to 1.5 µg/ml after the last dose. Gastric drug concentration meanwhile increased, reaching 539 µg/ml, or up to 300 times plasma concentration. This patient received 300 mg of meperidine over 2.75 hours.

Two of the seven patients studied in the third phase showed an intermittent decrease in gastric meperidine concentration; Fig 3 shows data from one of them. This patient's plasma concentrations varied between 1.7 and 5.5 µg/ml, while gastric concentrations ranged from slightly more than 1 to over 245 µg/ml. Gastric concentrations dropped early in the study from 157.6 to 104.2 µg/ml, while plasma drug concentrations rose from 1.7 to 3.0 µg/ml, before more meperidine was given. Later, a more precipitous fall in gastric concentration, from 245.6 to 8.2 µg/ml, was followed by a rise from 2.0 to 2.5 µg/ml in plasma levels. A third smaller rise occurred when gastric concentration approached plasma concentration. The dose of meperidine was 225 mg, given over 1.17 hours. The other patient had one moderate episode in which the gastric drug concentration fell, followed by a slight rise in plasma concentration.

TABLE 2
Time of First Detection of Meperidine in Gastric Contents

Patient	Meperidine present* at:		
	5 min	10 min	15 min
		µg/ml	
3	0	0	13.50
5	0	5.51	12.76
8	11.4†	24.60	36.80
18	0	0	5.99
20	6.24	17.60	193.30

* Meperidine present before meperidine administration was zero in all patients.

† Value at 8 minutes.

TABLE 3
Plasma and Gastric Meperidine Concentrations of Patients in Phase 3

Patient	Total meperidine administered	Length of study period	Plasma values after meperidine administration	Gastric juice values after meperidine administration
	mg	min	µg/ml	
2	550	370	0.76–2.02	1.33–60.96
3	300	485	1.06–3.16	0–539.00
7	400	390	1.45–4.07	0–503.00
11	400	360	0.40–1.54	1.15–339.80
12	475	110	0.26–2.18	2.49–66.73
19	325	296	1.55–2.60	1.83–61.50
20	225	272	1.71–5.50	1.02–245.64

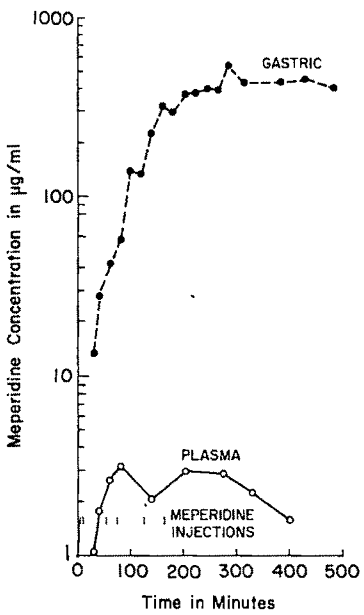

FIG 2. Meperidine concentrations in plasma and gastric juice of patient 3. Vertical bars designate times of meperidine injections in 50-mg increments.

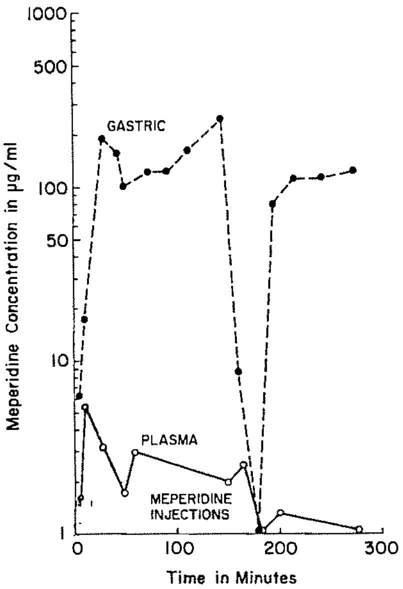

FIG 3. Fluctuations in levels of meperidine in plasma and gastric juice of patient 20. Vertical bars designate times of meperidine injections in 50-mg increments.

TABLE 4
Amounts of Meperidine Excreted in Gastric Juice

Patient	Sex/ wt.	Total meperidine recovered	Volume	Time of collection	Total meperidine administered
	kg	*mg*	*ml*		*mg*
3	F/48.6	2.0	20.7	3 hr 45 min	300
		14.4	62.5	8 hr 15 min	300
8	M/81.4	3.4	20.4	3 hr 45 min	350
		23.1	61.9	8 hr 40 min	350
9	F/121.6	6.4	62	6 hr	400
10	F/58	1.2	65.4	3 hr 45 min	400
11	M/62.5	1.6	27	2 hr 15 min	200
17	M/123.9	1.2	63	3 hr 45 min	1100

Phase four results are summarized in Table 4. Total volumes of gastric juice withdrawn were between 20 and 65 ml, or between 7 and 24 ml/hr. Total meperidine recovered during the study varied between 1.2 mg over 3.75 hours and 23 mg over 8.67 hours. Maximum recovery of unchanged drug was 4.8% of the administered dose.

Discussion

Our previous communication[1] noted the occurrence of gastric meperidine in high concentrations during the postoperative period. This study shows that significant sequestration of meperidine also occurs during the operative period. The drug appeared in the stomach within 15 minutes of intravenous administration, and occurrence increased continuously in most patients. Nitrous oxide and surgical manipulation apparently did not inhibit the process to any great extent. Drug washout by large gastric volumes also was not a factor in causing meperidine accumulation. Most patients, especially those undergoing abdominal surgery, secreted low volumes of gastric fluid.

Prolonged collection time and mean plasma level of drug appeared to be the most important determinants of the amount of meperidine collected. The longer the collection time, the greater the amount of meperidine recovered. Also, at the start of the study, when the mean plasma drug level was low, gastric accumulation was small. Thus, while patient 3 (Table 4) sequestered 14.4 mg of meperidine over 8.25 hours, she did this unevenly—2.0 mg during the first 3.75 hours and 7.9 mg in the final 4 hours. Similarly, whereas the amount of meperidine we collected from patient 8 over 8.7 hours was 23.1 mg, we obtained only 3.4 mg in the first 3.75 hours.

The accumulation of intravenously administered meperidine in gastric juice in concentrations greater than accumulations in plasma can best be explained by the mechanism of ion trapping. This is analogous to the phenomenon described by Shore and co-workers[3] for the basic compounds quinine and aniline. Meperidine, with a pKa of 8.7, is 57% ionized at pH 7.4, if we assume 40% is protein bound. In media with a pH of 1 it will ionize almost completely. Unionized meperidine readily diffuses across membranes such as gastric mucosa. In the stomach cavity, the drug ionizes and accumulates. A calculation of the theoretical ratio between gastric and plasma concentrations at equilibrium, using the Henderson-Hasselbalch equation, gives a value of 10^6 when the pH gradient is 6. Our highest ratio was about 400, indicating that under the conditions of our clinical study equilibrium was not obtained. Factors such as gastric emptying, blood flow through the stomach, and the rate of gastric juice production also probably interfered with its attainment. However, a tendency to build a high concentration was indicated repeatedly in our study. The data show that gastric concentrations of the drug continued to increase hours after the last incremental dose.

The intermittent decrease in gastric drug levels along with an increase in plasma levels suggest another aspect of meperidine kinetics (Fig 3). We interpret the decrease as being due to gastric emptying and the increase as being due to drug reabsorption. Intestinal secretions neutralized the gastric contents which passed through the pyloris, causing an increase in unionized meperidine. This in turn was reabsorbed. Mather et al[4] reported two patients with what they termed an anomalous secondary rise in plasma concentration—time curves following a single intravenous 50-mg dose of meperidine. The information given with one of these curves suggests drug reabsorption. It occurred during severe gastrointestinal spasm, 45 minutes after the drug injection had elicited a histamine release-flare. The rise in the second patient is suggestive of reabsorption, but the data are insufficient to allow definite conclusions. Further study over a longer time period is necessary before the frequency and possible clinical significance of this sequence of events can be determined.

Since our preliminary report appeared, Dunkerley et al[5] have confirmed our findings of meperidine accumulation in gastric contents. The gastric/plasma concentrations they recorded in awake human volunteers varied between 10 and 200 in the 4-hour period following a 50-mg intravenous dose. The same phenomenon has recently been reported for methadone and its major metabolite.[6]

In summary, the stomach serves as a reservoir for intravenously administered meperidine in humans. Up to 5% of the dose may be accumulated here. This phenomenon appears to be due to ionization of the drug by the acid gastric juice. The ionized meperidine becomes trapped in the stomach cavity and its concentration increases. The sequestration occurs early after drug administration since detectable amounts appear within 15 minutes. The mechanism for returning meperidine to the circulation appears to be related to gastric emptying into the intestine followed by neutralization of the ionized drug and reabsorption.

ACKNOWLEDGMENTS

Mr. James Ewing and Ms. Alice MacDonald provided the technical assistance.

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Nitroprusside and Myocardial Blood Flow

The effect of nitroprusside on regional myocardial specific blood flow (RMBF) was evaluated in 25 patients with the xenon-133 washout technique. Six patients were normal (group 1), six patients had coronary artery disease without collateral vessels (group 2), and 13 patients had coronary artery disease with collateral vessels (group 3). In group 1 RMBF remained unchanged following nitroprusside. RMBF decreased significantly in both group 2 and group 3, including seven patients in group 3 with high-grade collateral vessels. The results were compared to the effect of nitroglycerin in 31 patients previously studied using the same technique. Mean arterial pressure and pressure-rate product were comparably reduced by both drugs. In contrast to the findings with nitroprusside, after sublingual nitroglycerin RMBF decreased markedly in normal subjects and increased in patients with coronary artery disease and high-grade collaterials. The data suggest that nitroprusside may primarily affect resistance vessels within the coronary circulation, as opposed to the effect of nitroglycerin on conductance vessels. Thus, nitroprusside could result in redistribution of blood flow away from ischemic areas and potentially increase ischemic injury in some patients with coronary artery disease. *(Mann T, Cohn PF, Holman BL, et al: Effect of nitroprusside on regional myocardial blood flow in coronary artery disease: results in 25 patients and comparison with nitroglycerin. Circulation 57:732–738, 1978)*

ANESTH ANALG
58:93-98, 1979

Naloxone Fails to Antagonize Halothane-Induced Depression of the Longitudinal Muscle of the Guinea Pig Ileum

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SHIWAKU, Y., NAGASHIMA, H., DUNCALF, R. M., DUNCALF, D., AND FOLDES, F.: Naloxone fails to antagonize halothane-induced depression of the longitudinal muscle of the guinea pig ileum. Anesth Analg 58:93–98, 1979.

The influence of halothane, or naloxone, or halothane followed by naloxone was investigated in the in vitro myenteric plexus longitudinal muscle preparation of the guinea pig ileum. Halothane alone in 1.5 to 2.0% (v/v) concentration caused about 50% depression of the twitch and decreased both spontaneous acetylcholine (ACh) release ($p < 0.02$) and volley output of ACh ($p < 0.02$). Very high concentrations (>1 μM) of naloxone caused a nonspecific, postsynaptic depression of the twitch. Higher than 100 nM concentrations of naloxone increased spontaneous ACh release, but had no effect on the volley output of ACh. Over a wide concentration range, from 15 nM to 3 μM, naloxone did not antagonize in the longitudinal muscle preparation the effects of halothane on any of the parameters investigated. These findings indicate that the sites of action of halothane and naloxone in this preparation are not identical.

Key Words: ANTAGONISTS, Narcotic: naloxone; ANESTHETICS, Volatile: halothane.

IT IS well known that naloxone hydrochloride (naloxone) antagonizes both the central[1-3] and peripheral[4-6] effects of narcotic analgesics (narcotics). It has also been reported that naloxone in relatively large doses also antagonizes the central nervous system effects of such diverse substances as ethanol,[7] pentobarbital and methohexital,[8] and inhalation anesthetic agents, such as halothane[9] and nitrous oxide.[10] Recently, however, evidence has been presented that naloxone does not reverse the CNS effects of halothane.[11, 12] The investigations to be presented were undertaken to determine whether or not naloxone is capable of antagonizing one of the peripheral effects of halothane.

Methods and Material

Experimental Setup

The experiments were carried out on the isolated myenteric plexus longitudinal muscle preparation of

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the guinea pig ileum as described by Paton and Vizi.[13] The net weights of the 4- to 5-cm long strips used were 40 to 90 mg. The muscle strips were suspended in a jacketed organ bath of 4-ml capacity (Fig. 1) filled with mammalian Krebs' solution (NaCl, 113 nM; KCl, 4.7 nM; $CaCl_2$, 2.5 nM; KH_2PO_4, 1.2 nM; $MgSO_4$, 1.2 nM; $NaHCO_3$, 25 nM; and glucose, 11.5 nM). The distal end of the muscle strip was firmly attached with a thread to the organ bath, its proximal end with another thread to a Grass FT03C transducer. The Krebs' solution, kept at 37 C, was aerated with 95% O_2-5% CO_2, with or without halothane. Supramaximal square wave pulses of 1-msec duration were delivered from a Grass model S-88 stimulator at 0.1 Hz, through platinum electrodes placed at each end of the muscle strips. The potential drop between the two electrodes was 8 to 10 V/cm. The muscle strips were adjusted, to an initial resting tension of 1.0 g before the start of the experiments. This tension gradually declined during the 60-minute incubation period and became stabilized at 0.2 to 0.6 g. The twitch tension elicited was recorded on a Beckman type R Dynagraph at a paper speed of 5 mm/min.

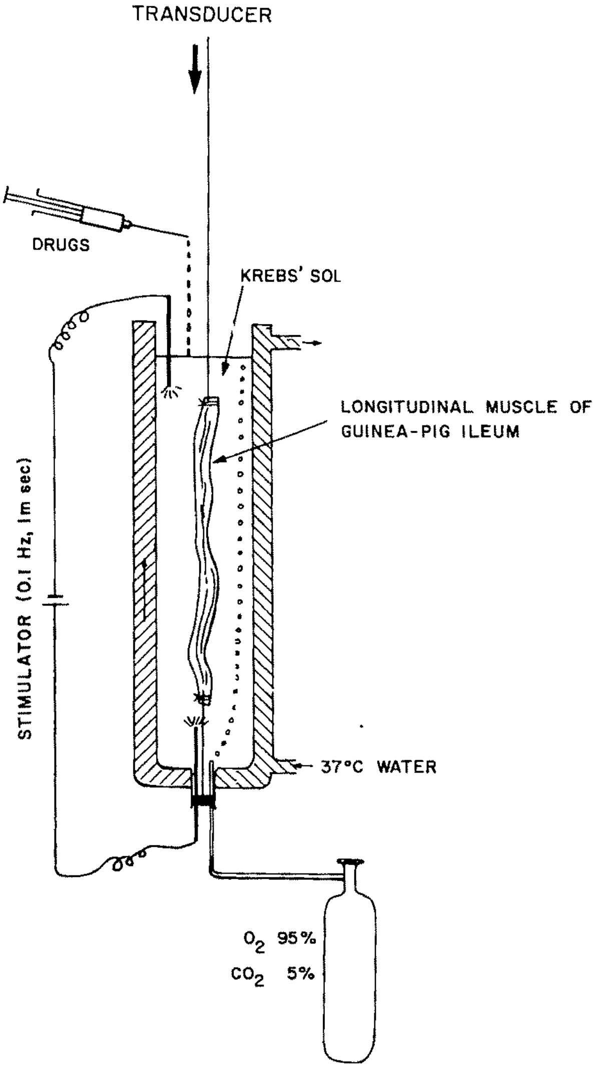
TRANSDUCER
DRUGS
KREBS' SOL
LONGITUDINAL MUSCLE OF GUINEA-PIG ILEUM
STIMULATOR (0.1 Hz, 1m sec)
37°C WATER
O_2 95%
CO_2 5%

FIG 1. Schematic representation of the experimental setup.

Halothane was delivered from a Fluotec Mark II vaporizer in concentrations, 1.5 to 2.0 v/v%, required to depress the twitch tension to 50% of control.

Fluid changes in the organ bath were effected rapidly by an overflow system.[13]

Selection of Dose Range of Naloxone

Finck et al[9] reported that 10 mg/kg SC naloxone antagonized the central nervous system effects of halothane in rats. This dose is about 200 times larger than the dose of naloxone required to antagonize morphine-induced apnea in rats (F. F. Foldes, unpublished data). Because of this, the influence of naloxone on the effects of halothane on the twitch tension, spontaneous (nonstimulated, resting) and stimulated acetylcholine (ACh) release and volley output was explored in a 200-fold 15 nM to 3 μM dose range. The 15 nM lower limit was selected because this concentration of naloxone almost completely antagonizes and prevents the depressant effects of narcotics on the electrically induced twitch of the longitudinal muscle of the guinea pig ileum (Fig. 2).

Measurement of Effect of Halothane and Naloxone on Twitch Tension

After 60 minutes of stabilization in Krebs' solution, about 50% steady state depression of the twitch tension was produced by adding the necessary concentration of halothane vapor to the O_2-CO_2 mixture. Subsequently, in the same experiments the halothane was discontinued and the preparation washed with fresh Krebs' solution. In other experiments, 3 μM naloxone was added to the bath after the development of the steady state halothane block. After observing the effect of naloxone, halothane administration was discontinued and the preparation was washed. For the sake of comparison, in other experiments the effect of 3 μM naloxone alone on the twitch tension was investigated.

Measurement of Effect of Halothane and Naloxone on Acetylcholine Release

In these experiments, 3 μM eserine sulfate was added to the Krebs' solution to inhibit the enzymatic

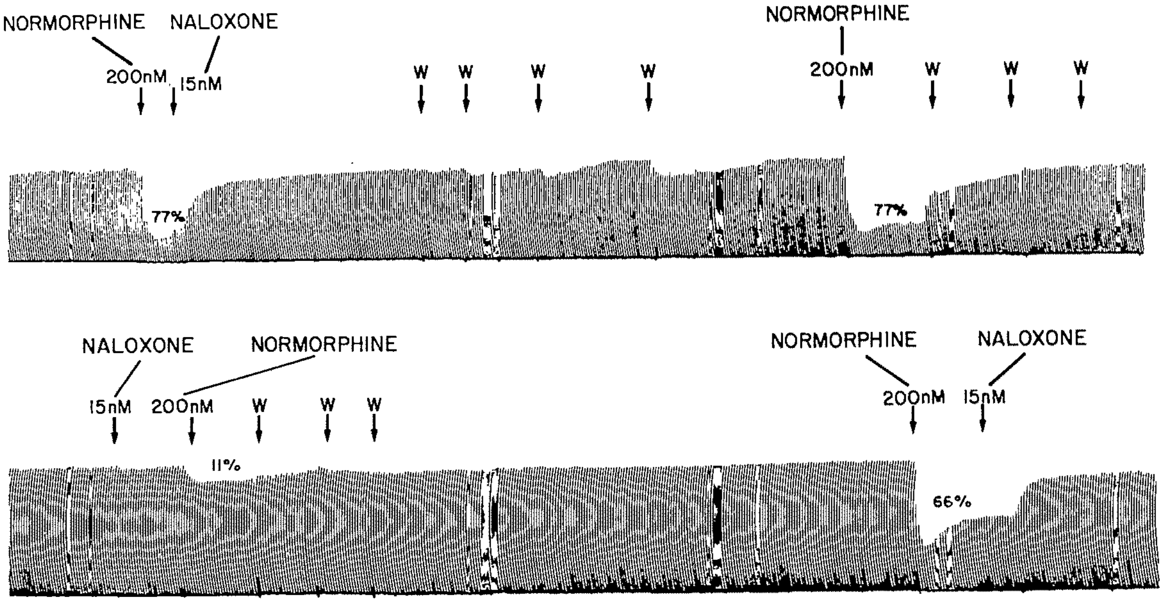

FIG 2. Antagonism and prevention of the narcotic-induced depression of the electrically elicited twitch of the myenteric plexus-longitudinal muscle preparation of the guinea-pig ileum. Note that 15 nM naloxone antagonizes and prevents the depressant effects of normorphine.

hydrolysis of the released ACh. Longitudinal muscle strips (total wet weight 180 to 300 mg) were suspended in one organ bath. In separate experiments, the effects of halothane, or 3 μM naloxone, or both, on spontaneous or stimulated ACh release were determined. Since 3 μM eserine causes contracture of the muscle and blocks the twitch (Fig. 3), the concentration of halothane that depressed the twitch by 50% was selected by observing the effect of halothane on another muscle preparation of the same ileum suspended and stimulated in eserine-free Krebs' solution which served as a monitoring strip.

After 60 minutes of equilibration in eserinized Krebs' solution, spontaneous and stimulated ACh release were determined in each preparation. Subsequently in some preparations, spontaneous and stimulated ACh release were assayed after a 20-minute equilibration of the eserinized Krebs' solution with concentrations of halothane that caused approximately a 50% depression of the twitch tension of the monitoring strip. In other experiments the muscle strips were equilibrated for 20 minutes after the addition of 3 μM naloxone to the bath, before determining the spontaneous and stimulated ACh release. Additionally, in other experiments spontaneous and stimulated ACh release were determined at first in the presence of halothane and subsequently in the presence of halothane and naloxone. At the end of each experiment spontaneous and stimulated ACh release were again determined after the preparations were allowed to equilibrate in fresh Krebs' solution for 20 minutes.

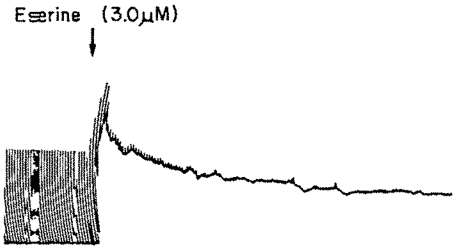

FIG 3. Influence of eserine on the myenteric plexus longitudinal muscle preparation of the guinea pig ileum. Note that the addition of eserine causes contracture of the muscle.

Bioassay of ACh

ACh was assayed on a length of guinea pig ileum suspended in Krebs' solution in the type of organ bath used for the collection of the samples according to the method of Paton and Vizi[13] and Vizi et al.[14] To prevent spontaneous contraction of the ileum, 15 μM morphine sulfate was added to the Krebs' solution, and a soft spring with a 1 g/cm compliance was interposed between the proximal end of the ileum and the transducer. Assay temperature was 33 C. ACh output of the longitudinal muscle was determined by measuring the contraction of the ileum caused by the addition of a 0.1- to 0.2-ml aliquot of the fluid, collected from the organ bath, to the assay bath. The contraction of the ileum that was caused by the sample was compared to the effects of known (2, 4, 8, and 16 ng) amounts of ACh-Br added to the bath. This was done by using a computer program designed for a Hewlett-Packard 97 desk calculator. The total amount of ACh (ACh_t) released during the 10-minute collection period was calculated from the formula:

$$ACh_t\,(ng) = ACh_s\,(ng) \times \frac{V_b}{V_s}$$

where ACh_s is the ACh content of the sample, V_b is the volume of fluid in the organ bath, and V_s is the volume of the sample. From this formula the spontaneous or stimulated ACh ($\rho mol \cdot g^{-1}\ min^{-1}$) released can be calculated with the formula:

$$ACh\ (\rho mol \cdot g^{-1}\ min^{-1}) = \frac{ACh \times 1000}{W \times 10 \times 226.4}$$

where W is the wet weight of the longitudinal muscle strips and 226.4 is the molecular weight of ACh-Br. From the spontaneous and stimulated ACh release volley output can be calculated: the formula,

volley output of ACh

$$= \frac{\text{stimulated ACh release} - \text{spontaneous ACh release}}{\text{number of stimuli during the collection period}}$$

It was demonstrated in preliminary experiments that the concentration of naloxone (0.075 to 0.15 μM) in the assay bath during the short periods required for the assay (<10 seconds) did not antagonize the inhibition of the spontaneous ACh release caused by the 15 μM concentration of morphine present in the assay bath. Consequently the presence of naloxone in the assay bath did not interfere with the accuracy of the assay.

Results

Concentrations up to about 1 μM naloxone had little or no effect on the twitch tension of the longitudinal muscle preparation of the guinea pig ileum (Fig. 4). Very high, 3 μM concentrations of naloxone however caused a moderate, but significant ($p < 0.05$) decrease of twitch tension (Table 1 and Fig. 4). The twitch remained below control even after washout.

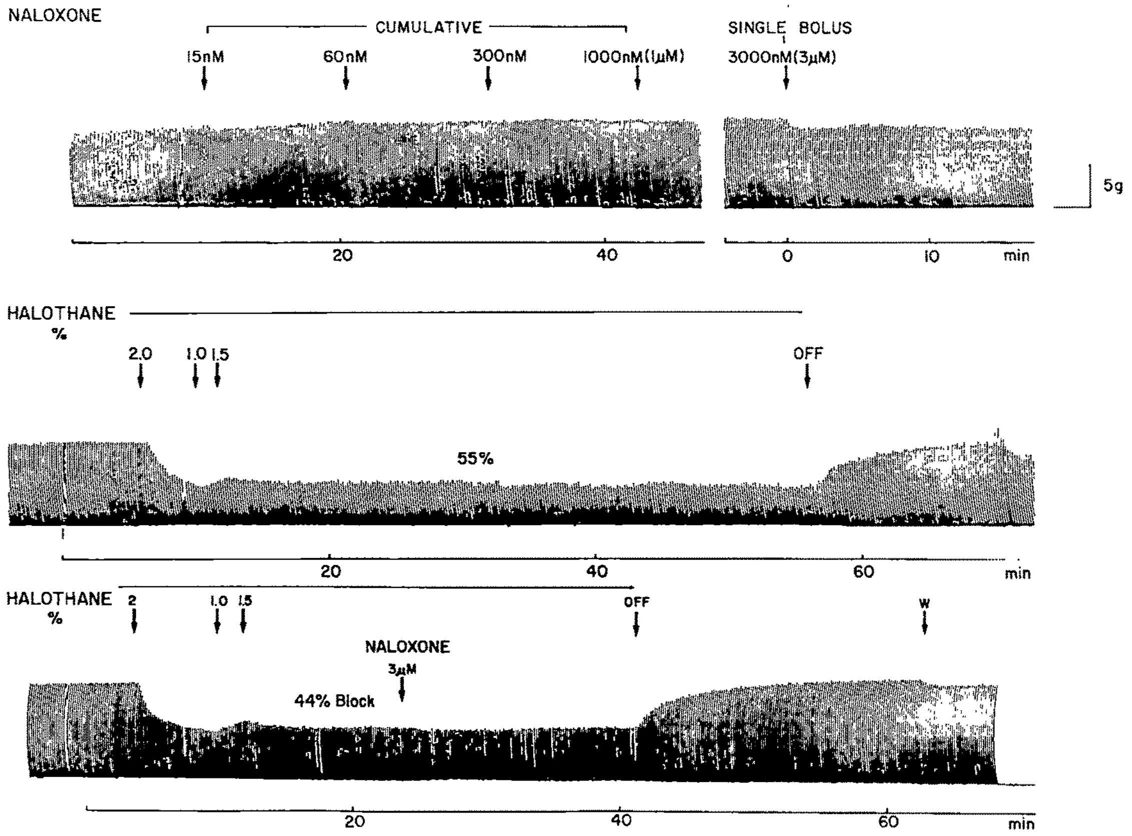

FIG 4. Influence of halothane, or naloxone, or halothane followed by naloxone on the twitch tension of the myenteric plexus longitudinal muscle preparation of the guinea pig ileum. Note that naloxone does not antagonize the halothane-induced depression of the twitch tension.

Furthermore, these large concentrations of naloxone had no influence on the halothane-induced depression of the twitch tension (Table 1 and fig 4).

Halothane in concentrations that produced a 50% depression of the twitch of the control muscle strip depressed (Table 2) spontaneous ($p < 0.05$) and stimulated ($p < 0.02$) ACh release and volley output ($p < 0.02$). Spontaneous release remained depressed ($p < 0.05$) after washout of halothane. However, the stimulated ACh release and the volley output after washout were not significantly different from control.

TABLE 1
Influence of Halothane, or Naloxone, or Both on Electrically Induced Twitch Tension of Longitudinal Muscle of Guinea Pig Ileum

Agent	Twitch tension (% of control)*	
	With agents	After washout
Halothane‖	50.1 ± 2.7 (5)	89.2 ± 5.8
Naloxone (3 μM)	92.8 ± 2.3† (7)	91.0 ± 2.1§
Halothane + naloxone	52.4 ± 5.4 (7)	97.3 ± 6.2

* Values are means ± SEM. Number of experiments is shown in parentheses.
† Significant difference from control at the $p < 0.05$ levels.
§ Significant difference from control at the $p < 0.01$ level.
‖ Bath equilibrated with 1.5 to 2.0% (v/v) halothane.

In contrast to its effect on twitch tension, naloxone instead of decreasing, increased spontaneous ($p < 0.02$) and stimulated ($p < 0.02$) ACh release, but had no effect on volley output. After washout, spontaneous ACh and stimulated ACh release returned to control ($p < 0.05$) and volley output remained at control.

The halothane-induced depression ($p < 0.01$) of spontaneous and stimulated ACh release and volley output was not antagonized by naloxone (Table 3). After washout of both agents, spontaneous release remained depressed ($p < 0.02$); stimulated release and volley output, however, were not significantly different from control.

Discussion

A similar depression of the twitch by high concentrations of naloxone was also observed by Kosterlitz

TABLE 2
Influence of Halothane or Naloxone on Acetylcholine Output of Myenteric Plexus Longitudinal Muscle Preparation of Guinea Pig Ileum

Type of release	Acetylcholine output in presence of*					
	Halothane			Naloxone		
	Control	With agent	After washout	Control	With agent	After washout
Spontaneous (ρ mol/g/min)	690.4 ± 76.0	565.3 ± 64.1†	465.0 ± 33.2†	506.5 ± 41.1	716.0 ± 80.9‡	608.6 ± 37.1
Stimulated‖ (ρ mol/g/min)	1118.7 ± 127.3	706.8 ± 45.1‡	954.7 ± 76.5	880.0 ± 76.5	1081.1 ± 96.8‡	972.4 ± 73.4
Volley output (ρ mol/g/volley)	71.2 ± 10.2	27.0 ± 2.7‡	80.9 ± 8.4	62.3 ± 10.2	62.3 ± 7.5	60.6 ± 13.3

* Values are means ± SEM of four experiments.
† Significant difference from control at the $p < 0.05$ level.
‡ Significant difference from control at the $p < 0.02$ level.
‖ Stimulation rate 0.1 Hz.

TABLE 3
Combined Effect of Halothane and Naloxone on Acetylcholine Output of Myenteric Plexus Longitudinal Muscle Preparation of Guinea Pig Ileum

Type of release	Acetylcholine output*			
	Control	Halothane	Halothane + naloxone	After washout
Spontaneous (ρ mol/g/min)	556.0 ± 37.1	412.8 ± 30.5†	408.4 ± 25.6§	418.6 ± 34.5‡
Stimulated‖ (ρ mol/g/min)	781.0 ± 37.5	523.3 ± 19.0§	541.9 ± 33.4§	830.1 ± 60.1
Volley output (ρ mol/g/volley)	46.9 ± 7.1	15.2 ± 2.7§	22.1 ± 2.7‡	68.5 ± 7.5§

* Values are means ± SEM of seven experiments.
† Significant difference from control at the $p < 0.05$ level.
‡ Significant difference from control at the $p < 0.02$ level.
§ Significant difference from control at the $p < 0.01$ level.
‖ Stimulation rate 0.1 Hz.

and associates.[15, 16] They demonstrated that high concentrations of naloxone inhibited the contraction caused by exogenous ACh or histamine and from this they concluded that the depression of twitch caused by high concentrations of naloxone is a nonspecific, postjunctional effect. This is in contrast to the effect of narcotics which depress the twitch by inhibiting presynaptic release of endogenous ACh and which can be antagonized by a low, 15 nM, concentration of naloxone (Fig. 2).

As observed earlier by others (H. W. Kosterlitz, personal communication) higher than 50 nM concentrations of naloxone increase spontaneous ACh release but have no effect on volley output of ACh. The increase of stimulated release caused by naloxone could be attributed to the increase of its spontaneous component. This explains why the twitch was depressed by naloxone, despite the increase of the stimulated ACh release.

Halothane, in contrast to naloxone, depressed both spontaneous ACh release and volley output of ACh. It is of interest that while spontaneous ACh release remained depressed, the volley output of ACh returned to its control value after washout (Table 2). This finding and the observation that naloxone only enhanced spontaneous ACh release indicate that the site and/or mechanism of spontaneous ACh release and volley output of ACh are different. This assumption is further corroborated by the failure of naloxone to influence even in very high concentrations (up to 3 μM) the depressant effects of halothane on twitch tension (Table 1 and Fig. 4) and spontaneous ACh release and volley output of ACh (Table 3).

In conclusion, the observations made in this study indicate that naloxone, even in very high concentrations, is unable to antagonize the depressant effect of halothane on the myenteric plexus of the longitudinal muscle preparation of the guinea pig ileum. These findings parallel those of Harper et al[11] and Bennett[12] who made similar observations of the lack of antagonism by naloxone of CNS effects of halothane.

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Failure of Lidocaine to Trigger Porcine Malignant Hyperthermia

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WINGARD, D. W., AND BOBKO, S.: Failure of lidocaine to trigger porcine malignant hyperthermia. Anesth Analg 58:99–103, 1979.

Lidocaine, considered by some to be potentially dangerous in malignant hyperthermia (MH), was administered intravenously to a dose of 15 mg/kg to five conscious MH-susceptible pigs. Subsequently the same pigs were given 24 mg/kg intravenously over a period of 2 hours after being anesthetized with thiopental. All animals developed systemic toxicity to lidocaine but without evidence of MH. Prior administration of lidocaine did not prevent development of subsequent MH due to succinylcholine and halothane. Lidocaine is safe in porcine MH.

Key Words: HYPERTHERMIA: malignant pyrexia ANESTHETICS, Local: lidocaine.

AMIDE-TYPE local anesthetics such as lidocaine are considered hazardous in malignant hyperthermia (MH)-susceptible patients[1] because these anesthetics enhance contraction coupling of skeletal muscle.[2,3] Hall et al[4] described hind limb convulsive motion in MH-susceptible Landrace swine given lidocaine intramuscularly. Lidocaine has, however, been used in man without harm during MH crises.[5,6] Lidocaine has also been used successfully for peridural anesthesia in MH-susceptible swine[7] and has been used repeatedly for local anesthesia in MH-susceptible patients (D. W. Wingard, unpublished results). Because of this conflicting evidence, the following studies were performed to determine the effect of intravenous lidocaine on porcine MH.

Method

Two male and three female crossbred Poland China/Large White MH-susceptible swine were studied. The swine, weighing 34 to 88 kg each, were fed a standard swine diet and were receiving no medications. All five were given lidocaine intravenously on two separate occasions at least 1 week apart.

Experiment 1

Each unmedicated pig was restrained with a snout holder. An ear vein was cannulated with an indwelling no. 18 plastic cannula for administration of lidocaine. Rectal temperatures were recorded with a model 47 Yellow Springs thermistor before and after the administration of lidocaine. Venous blood samples were withdrawn from the ear vein for determination of serum Na^+, K^+, P_{CO_2}, P_{O_2}, and pH after injection of lidocaine (Astra). Lidocaine 4% without preservatives was injected at a rate of 0.6 mg/kg/min until grand mal seizures occurred or until 15 mg/kg were injected. The maximum time of injection was 25 minutes.

Experiment 2

After restraining the animal with a snout holder, a total of 26 mg/kg of 5% thiopental sodium was administered intravenously via a cannulated ear vein to induce and maintain anesthesia during the preparation period, but none was given within 20 minutes of beginning lidocaine infusion. The trachea was intubated and respiration was controlled with a Mörch respirator using room air. A percutaneous central

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venous catheter was inserted for periodic measurement of mixed venous P_{O_2}, P_{CO_2}, pH, Na^+, K^+, phosphate, lactate, and pyruvate. The animals were continuously monitored with an ECG and rectal temperature probes. Blood pressure and pulse were recorded every 5 minutes by indirect methods from the right foreleg. Both intravenous catheters were kept patent with a slow infusion of Ringer's lactate solution.

Forty minutes after induction of anesthesia, control blood samples were obtained and an infusion of Ringer's lactate containing 2 mg/ml of lidocaine without preservatives was administered over 2 hours at a rate of 0.2 mg/kg/min to provide a total dose of 24 mg/kg. Blood samples were obtained at 15-minute intervals.

After 120 minutes the lidocaine infusion was stopped and the animals received 0.88 mg/kg of intravenous succinylcholine. Ten minutes later, 6% halothane in oxygen was administered for induction of anesthesia from an Ohio 5000 anesthesia machine in a non-rebreathing system. Anesthesia was maintained at 2 to 4% halothane. Halothane was discontinued after well established MH occurred but not until a 0.5 C rise in rectal temperature.

The data are expressed as mean values ± the standard error of the mean. Statistical significance ($p < 0.05$) was determined using the Student's *t*-test.

Results

None of the swine developed clinical or metabolic signs of MH during the lidocaine infusions. In experiment 1, all animals responded to the rapid infusion in essentially the same manner. After approximately 1 mg/kg of lidocaine, they became quiet, and after 2 mg/kg they became stuporous, unstable, and sank to the floor. After 4 mg/kg of lidocaine, they appeared to be asleep but responded to noise and moderately painful stimulation. After 6 to 8 mg/kg of lidocaine, muscle twitching occurred; this became progressively worse as the infusion continued. Two animals developed grand mal seizures; one of these animals had a period of transient apnea and cyanosis. Within minutes of completion of lidocaine injections, all animals were lying in a calm, stuporous state with quiet rhythmic breathing. All pigs recovered and were ambulatory in 30 to 120 minutes. Venous blood gas tensions and rectal temperature indicated absence of MH (Table).

TABLE

Effect of Lidocaine (0.6 mg/kg) on Rectal Temperature and on Peripheral Venous Electrolytes and Blood Gases of MH-Susceptible Swine (Mean ± SEM)

Temperature (C)	
Control	38.3 ± 0.5
After lidocaine	37.9 ± 0.3
Electrolytes (mEq/L)	
Na^+	133 ± 3.1
K^+	3.7 ± 0.2
Peripheral venous blood gas tensions (mm Hg)	
P_{O_2}	67 ± 4.4
P_{CO_2}	34 ± 1.1
pH	7.43 ± 0.02

The results of the 2-hour infusion of lidocaine (experiment 2) followed by succinylcholine and halothane are seen in Figs 1 and 2. In none of the animals did lidocaine trigger MH. All five pigs developed muscle twitching followed by clonic seizure activity after 6 to 8 mg/kg of lidocaine, but none developed grand mal seizures. All measured variables remained essentially unchanged except the heart rate and body temperature, both of which fell significantly during the 2 hours ($p < 0.05$). Following succinylcholine, violent muscle fasciculations occurred followed by good muscle relaxation with a marked elevation of serum lactate and pyruvate. Halothane caused the appearance of clinical MH with a marked change in all of the parameters except the body temperature. One animal died after 156 minutes (36 minutes after succinylcholine, 26 minutes after halothane), another after 166 minutes, and a third after 168 minutes. The anesthetic was not discontinued prior to death because none of these three animals met our criteria of a 0.5 C rise in rectal temperature prior to death. A fourth 81-kg animal received 100 mEq of sodium bicarbonate, 20 mg of haloperidol, and 900 mg of procainamide, but died 46 minutes after initiating therapy. The temperature of this animal had risen 3.3° by the time of death; mixed venous blood gases were P_{CO_2}, 104 mm Hg; P_{O_2}, 37.1 mm Hg; and pH 7.10 at the time therapy was begun, and 148, 17.3, and 6.85, respectively, at the time of death. The fifth pig was the only survivor. The temperature in this animal eventually rose 1.5° from 35.2 to 36.7 C where it stabilized following lidocaine. When halothane was discontinued mixed venous gases were P_{CO_2}, 103 mm Hg; P_{O_2}, 35 mm Hg; and pH 7.05. This animal was treated with 300 mEq of sodium bicarbonate and 2900 mg of lidocaine administered in 100 to 400-mg boluses over 26 minutes. Muscle relaxation began 90 seconds after the second bolus of 200 mg of lidocaine. The muscle relaxation was complete after 2000 mg. The heart rate progressively slowed as the dose of lidocaine increased, and venous blood gases returned to normal (P_{CO_2}, 35 mm Hg; P_{O_2}, 38 mm Hg; pH 7.43),

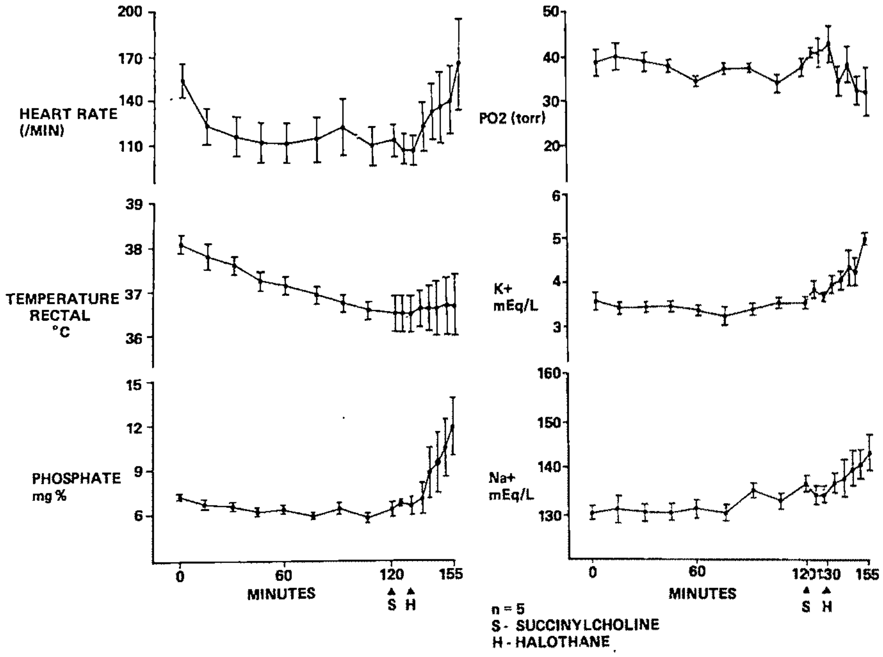

FIG. 1. Effect of 2 hours of a continuous intravenous lidocaine drip (24 mg/kg) on heart rate, rectal temperature, $P\bar{v}_{O_2}$, and serum sodium, potassium, and phosphate (mean ± SEM) in MH-susceptible swine before and after succinylcholine and halothane.

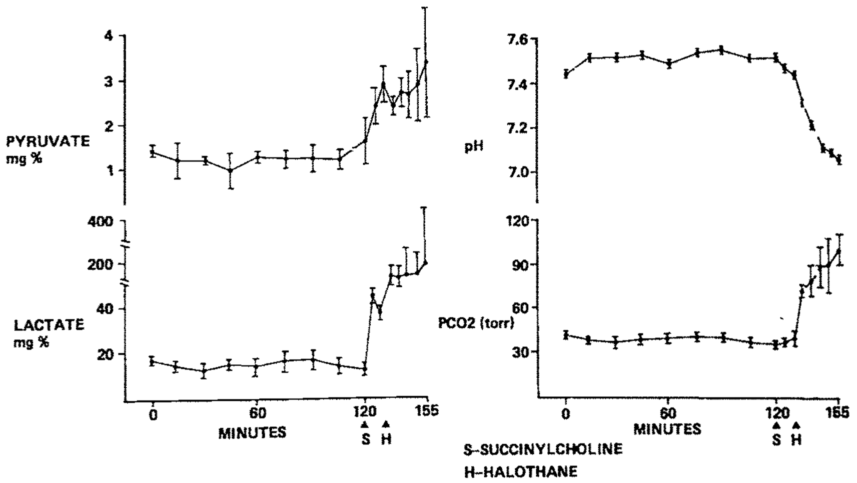

FIG. 2. Effect of 2 hours of a continuous intravenous lidocaine drip (24 mg/kg) on venous pyruvate, lactate, pH, and P_{CO_2} (mean ± SEM) on porcine MH before and after succinylcholine and halothane.

as did serum electrolytes. No attempt was made to cool any of the animals.

Discussion

We have been using lidocaine routinely for the past 3 years to provide local and block anesthesia in MH-susceptible swine.[7] In none of the animals has lidocaine triggered clinical MH. The present study was undertaken to determine whether there are metabolic changes typical of MH associated with the systemic infusion of lidocaine. The results substantiate the previous impressions that lidocaine does not trigger porcine MH. With doses high enough to produce seizure activity, intravenous lidocaine caused no clinical or laboratory evidence of MH. The only significant changes were a fall in heart rate and rectal temperature, both of which are opposite of that usually seen with MH. Hall et al[4] observed convulsive action in one MH-susceptible Landrace pig following intramuscular injection of 27 mg/kg of lidocaine. It is not clear from their description whether the convulsive movement was secondary to the CNS effects of lidocaine or was a manifestation of MH. However, at that dosage it is likely that these were toxic convulsions due to a high lidocaine blood level. As in our study, their pig developed MH upon subsequent inhalation of halothane.

The state of the pig prior to anesthesia influences the ease of triggering MH (D. W. Wingard, unpublished results).[8] Restraining the animals with a snout holder and inserting a cannula into the ear increases the likelihood of precipitating MH in animals that are not premedicated, presumably by inducing stress. If lidocaine triggers or potentiates MH, it should cause MH under these conditions, especially in doses causing muscle twitching and seizures. In experiment 1, the lidocaine did not potentiate or trigger clinical MH. Originally, it was our intention to monitor central venous metabolic changes throughout, but technical difficulties with insertion of monitors plus loss of all monitoring during seizure activity in two animals precluded obtaining central blood samples adequate for statistical analysis. However, those blood samples (not reported) which were collected prior to losing central venous lines also failed to demonstrate any abnormalities. We have observed that peripheral venous blood from the ear can be used to follow the course of MH. We prefer central venous blood because it is easier to collect multiple blood samples from the central veins. The decrease in body temperature and normal chemical values immediately following injection substantiate the clinical absence of MH.

In experiment 2, under more controlled circumstances using thiopental anesthesia, the infusion of several grams of lidocaine over 2 hours did not trigger MH. Again, these data substantiate previous experience that lidocaine nerve block and local anesthesia are safe in MH-susceptible swine. The thiopental appeared to have minimal effect because the animals were beginning to awaken when the lidocaine drip was begun and seizure activity appeared after 6 to 8 mg/kg of lidocaine as it did without thiopental in experiment 1. The response to succinylcholine with fasciculations and relaxation was typical of that seen in normal pigs. The elevation of serum lactate levels can be attributed to violent muscle contraction following injection of succinylcholine; the response to succinylcholine of our MH-positive pigs anesthetized with a "triggering" agent has always been fasciculation followed shortly by an increase in muscle rigidity. We have not observed skeletal muscle relaxation with succinylcholine in the presence of triggering anesthetic agents. Lidocaine appears to be similar to procaine[9] in that it did not prevent succinylcholine- and halothane-induced MH.

These data demonstrate that death from severe metabolic derangements and cardiovascular collapse in MH-susceptible swine can occur with minimal changes in rectal temperature and while the animal is hypothermic. Rectal temperature changes lag behind esophageal and tympanic temperature changes and do not accurately reflect immediate changes in core temperature. Rectal temperatures were used because of the ease of obtaining the temperature by this route in awake animals. It is possible that other sites for monitoring of temperature would have shown a greater change in body temperature.

The only survivor in experiment 2 was treated with an additional 2900 mg of lidocaine during an MH crisis for a total of 4900 mg of lidocaine. This is interesting because we have not been able to save several hundred other swine without the administration of dantrolene or vigorous therapy with cooling, hyperventilation, fluids, and sodium bicarbonate once an MH crisis has become fully established. The short time (90 seconds) between the initiation of lidocaine therapy and the onset of muscle relaxation suggests a causal relationship between lidocaine and survival. Further studies are under way to determine whether lidocaine is beneficial in the treatment of porcine MH.

These data do not prove that lidocaine is safe in MH-susceptible patients. However, lidocaine has been used in the treatment of human MH without any apparent adverse effects.[5,6] Zsigmond[10] infused 500 mg of lidocaine intravenously into an MH-susceptible patient without adverse response of MH. Since amide-type local anesthetics are the most commonly used group of local anesthetics for regional anesthesia, they have been used frequently in MH-susceptible individuals (D. W. Wingard, unpublished results). We are not aware of any deaths due to MH associated with lidocaine in these individuals. In light of recent evidence that MH may also be a sudden death syndrome in man related to stress,[11] it could be anticipated that there would be evidence of lidocaine enhancement of MH, especially when used in dental work where the anxiety level is high. The fact that there are no such reports suggests that lidocaine may be relatively safe in MH-susceptible individuals.

In summary, lidocaine is safe in MH-susceptible swine. Lidocaine causes neither clinical manifestations of MH nor chemical and blood gas changes typical of MH. This substantiates our previous clinical experience of the safety of lidocaine for regional anesthesia. However, lidocaine like procaine did not appear to protect the animals from subsequent "triggering" of MH by halothane and succinylcholine.

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Risk of Heart Block During Surgery

The risk of advanced atrioventricular block during anesthesia was studied prospectively in 44 patients with right bundle branch block and left axis deviation who underwent a total of 52 operations over a 14-month period. All patients had continuous electrocardiographic monitoring throughout anesthesia induction, operation, and surgical recovery. Of the 52 operative procedures, 24 were done using general anesthesia, 11 spinal, and 17 local infiltration. The preoperative cardiac rhythms included atrial fibrillation in two patients, atrial tachycardia with block in one patient, atrial flutter in one patient, and sinus rhythm in the remaining patients. Temporary pacemakers were inserted preoperatively in six patients, usually because of PR interval prolongation on the electrocardiogram. There was only one episode of transient complete heart block during the 52 operative procedures. In two of the six patients with temporary pacemakers, significant pacer-related ventricular irritability occurred. This study indicates that temporary pacemaker insertion is rarely required in patients with chronic right bundle branch block and left axis deviation who require noncardiac surgery. The authors continue to recommend the preoperative placement of temporary pacemakers in patients with the additional history of syncope, unstable angina pectoris, or recent myocardial infarction. *(Pastore JO, Yurchak PM: The risk of advanced heart block in surgical patients with right bundle branch block and left axis deviation. Circulation 57:677–680, 1978)*

ANESTH ANALG
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Abuse of Nitrous Oxide

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ROSENBERG, H., ORKIN, F. K., AND SPRINGSTEAD, J.: Abuse of nitrous oxide. Anesth Analg 58: 104–106, 1979.

The results of an anonymous questionnaire showed that up to 20% of medical and dental students have utilized nitrous oxide in a social setting to produce a "high." Nitrous oxide was obtained from a variety of sources, most often from cylinders used in the production of whipped cream. Although none of the 524 respondents described personal injury with the use of nitrous oxide, a few individuals reported cyanosis, nausea, and syncope.

Key Words: ANESTHETICS, Gases: nitrous oxide.

"*. . . I felt a high, an extraordinary degree of pleasure, different from that produced by wine . . . and yet approaching nearer to it than any other sensation I am acquainted with.*" [Description of nitrous oxide inhalation by Mr. James Thomson in the classic monograph of Sir Humphrey Davy[1]]

IN 1800 Humphrey Davy[1] first described the euphoric and analgesic qualities of nitrous oxide. Since the late 19th century nitrous oxide has been used to produce analgesia in the operating room and dental operatory. In more recent times this gas has been found to be useful in industry (especially the dairy industry) as a mixing and foaming agent because it is nonflammable, bacteriostatic, and does not impart taste or odor to the food with which it is mixed.[2, 3]

Much as in Davy's time, N_2O is sometimes used by students in health professions for its euphoric effects.[4] We were interested in assessing the incidence and possible abuse potential of nitrous oxide as well as the sources of nitrous oxide when used in social settings.

Methods and Results

An anonymous questionnaire was distributed to and collected from medical and dental students at a nearby university following a lecture on unrelated material. Even though the distribution was limited in some instances, the response rate was high. The questions asked were: Have you ever inhaled nitrous oxide? If so, in a dentist's office, in a hospital setting, or in a social setting? What was the source of nitrous oxide? Were there any untoward effects?

The results of this questionnaire are shown in Tables 1 and 2. Depending on the class year, nitrous oxide is or has been used in a social setting by 8.5 to as many as 20% of students. Nitrous oxide was obtained in several ways. Most often, whipped cream cans or cartridges were mentioned as the source of the drug. However, tanks of nitrous oxide obtained from medical or commercial sources were also used. There was no greater incidence of nitrous oxide abuse in those who have had nitrous oxide previously either in the dental office or in the hospital. Although dental students may have greater access to nitrous oxide than medical students, we found no significantly different incidence in the use or abuse of this drug.

Most students reported that the experience was pleasant and without ill effects. However, there were occasional adverse effects. Nausea was reported by

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TABLE 1
Use of N_2O by Medical and Dental Students

	Total responses	N_2O used in social settings	Year of questionnaire
Medical students			
Class of 1980	32	5 (16%)	1976
Class of 1981	82	7 (8.5%)	1977
Class of 1982	137	23 (17%)	1978
Dental students			
Class of 1979	129	18 (14%)	1977
Class of 1980	64	13 (20%)	1977
Class of 1981	80	18 (14%)	1977

TABLE 2
Sources of N_2O Used in Social Settings

	Tanks (industrial-medical)	Whipped cream cans or cartridges	Unspecified
Medical students			
Class of 1980	3	2	0
Class of 1981	2	3	2
Class of 1982	6	13	4
Dental students			
Class of 1979	11	9	1*
Class of 1980	4	4	5
Class of 1981	3	8	2

* More than one source was indicated by some respondents

eight students, cyanosis was reported by one, and "uncomfortable feelings" by three. In particular, one respondent said that some of his friends had fainted and fallen during the use of nitrous oxide but apparently none were injured.

Discussion

In certain cases, nitrous oxide may pose a significant danger to those using this drug. For example, a person who has recently ingested alcohol and has a full stomach may enter an excitement stage of anesthesia upon inhaling nitrous oxide and possibly vomit and aspirate. (We did not document the incidence of concomitant drug and alcohol use with this questionnaire.) Since nitrous oxide in social settings is inhaled directly, without dilution with oxygen, prolonged inhalation of the drug may cause significant degrees of hypoxia which may precipitate arrhythmias. Furthermore, nitrous oxide may not be the sole constituent of the propellants used. For example, 10% CO_2 is frequently added[3] as well as halogenated hydrocarbon compounds (e.g. chloropentafluoroethane in "Reddi-Wip").

Toxicity from halocarbon propellants includes depression of myocardial contractility and sensitization of the myocardium to epinephrine, bronchospasm, and hypotension.[5]

A recent report[6] describes nerve damage characterized by numbness in the extremities, sluggish reflexes, and paresthesias, following habitual nitrous oxide abuse even when mixed with adequate amounts of oxygen. Interestingly, five of the patients so described were dentists and the sixth was a hospital technician. All of these individuals had ready access to inhalation anesthetics, an element in the abuse of other anesthetics by hospital personnel.[7]

Abuse of nitrous oxide may be widespread since its ability to produce a prompt evanescent "high" has been described and lauded in some college and general circulation newspapers.[4, 8] A recent article in the New York Times[9] described how easy it is to obtain nitrous oxide as well as other mind-altering drugs from "head shops." On college campuses it may be possible to buy whipped cream propellant cartridges (e.g. "whippets") from which about 3.5 L of nitrous oxide may be released. Similarly, by carefully tilting consumer whipped cream cans, up to 1.5 L of nitrous oxide may be released before topping is extruded.[3] Large nitrous oxide cylinders and reducing valves have been stolen from hospitals to furnish "laughing gas" for extracurricular student use.[10] Usually the gas is collected in a balloon and then inhaled from the balloon directly.

The approaching government ban on chlorofluorocarbons in aerosol products[11] may increase the use of nitrous oxide whose high solubility may be advantageous in some of these products.

Nitrous oxide is therefore used (or abused) in social settings among professional school students. Heretofore unreported in terms of incidence, the abuse of nitrous oxide by students may be even more prevalent than the 8.5 to 20% noted here, given the possibility of underreporting. The incidence of nitrous oxide abuse may vary, of course, in different student populations. Because of its potential dangers, we believe that more effective controls of the distribution of this drug should be instituted.

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Depression of Ventilation by Dopamine

Dopamine is present in the carotid body and has been postulated to be an inhibitory neurotransmitter. The purpose of this study was to determine the effects of dopamine on ventilation in man and to examine its mechanism of action. Dopamine (0.5 to 10 μg/kg/min) was infused in eight normal men (19 to 25 years) at different levels of arterial chemoreceptor activity, produced by varying the inspired P_{O_2}. During normoxia dopamine produced a small decrease in minute ventilation (VE) and an increase in arterial P_{CO_2}. When arterial chemoreceptors were stimulated by hypoxia, infusion of dopamine produced a marked initial depression of VE followed by a sustained although less pronounced decrease in VE. An increase in Pa_{CO_2} and a decrease in Pa_{O_2} were also observed. When arterial chemoreceptor activity was suppressed by hyperoxia, infusion of dopamine did not affect ventilation. Subjects also breathed a hypercarbic, hyperoxic gas mixture. The hypercarbia produces hyperventilation by stimulating central chemoreceptors, whereas the hyperoxia suppresses peripheral chemoreceptors. Dopamine did not alter ventilation while the subjects were breathing this gas mixture. These studies suggest that dopamine suppresses ventilation in man through an action on the arterial chemoreceptor reflex. These findings support the hypothesis that dopamine is an inhibitory neurotransmitter in the carotid body, and that release of dopamine may modulate the sensitivity of peripheral arterial chemoreceptors. *(Welsh MJ, Heistad DD, Abboud FM: Depression of ventilation by dopamine in man: evidence for an effect on the chemoreceptor reflex. J Clin Invest 61:708-713, 1978)*

ANESTH ANALG
58:107-115, 1979

Mutual Potentiation of the Neuromuscular Effects of Antibiotics and Relaxants

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BURKETT, L., BIKHAZI, G. B., THOMAS, K. C., JR., ROSENTHAL, D. A., WIRTA, M. G., AND FOLDES, F. F.: Mutual potentiation of the neuromuscular effects of antibiotics and relaxants. Anesth Analg 58:107–115, 1979.

The interaction of *d*-tubocurarine, pancuronium, or succinylcholine with neomycin, streptomycin, or polymyxin B was investigated using a rat phrenic nerve-hemidiaphragm preparation. All neuromuscular blocking agents (relaxants) mutually potentiated the neuromuscular blocking action of one another; combinations of ineffective concentrations of relaxants and antibiotics caused an 82 to 98% neuromuscular block. This extensive potentiation of the neuromuscular effects of relaxants by antibiotics can be attributed to the fact that antibiotics not only have a curare-like stabilizing effect on the postjunctional membrane, but also decrease presynaptic acetylcholine release. Neostigmine (0.25 μg/ml) only partially antagonized the neuromuscular block caused by the various drug combinations. In contrast, 4 μg/ml of 4-aminopyridine returned the twitch tension, depressed by combined administration of relaxants and antibiotics, to or above control values except in the case of neuromuscular block caused by the combinations of succinylcholine and polymyxin B.

Key Words: ANTIBIOTICS: neuromuscular junction; ANTIBIOTICS: interaction with muscle relaxants; MUSCLE RELAXANTS: interaction with antibiotics; INTERACTIONS (DRUG): antibiotics and relaxants.

IT WAS first noted in 1946 that the intravenous administration of large doses of streptomycin caused respiratory paralysis in mice[1] and that the animals could be saved by artificial ventilation.[2] Although these findings indicated that streptomycin may have neuromuscular blocking activity the systematic investigation of the neuromuscular effects of this compound only started in 1957.[3] By this time four cases of apnea had been reported following the intraperitoneal administration of neomycin in surgical patients anesthetized with ether.[4] Two of these patients were babies who did not survive. Numerous clinical reports and review articles have subsequently been published on the severe respiratory depression observed in surgical patients after intraperitoneal administration of antibiotics.[5-9] Most of these patients also received neuromuscular blocking agents during surgery. By 1974 at least 12 different antibiotics had been implicated. Since 1957 considerable experimental work has been carried out on a variety of animals regarding the relative potency and probable mechanism of the neuromuscular blocking actions of antibiotics, on the interaction of antibiotics and neuromuscular blocking agents (relaxants), and on the reversibility of the antibiotic-induced neuromuscular

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block by anticholinesterases and/or Ca^{2+}. Reviews of these publications, [9-11] indicate that there is still considerable difference of opinion regarding the site and mechanism of the neuromuscular activity of antibiotics.

The purposes of the present investigation were 2-fold: (1) to obtain quantitative information on the mutual potentiation of the neuromuscular effects of three antibiotics (neomycin sulfate, streptomycin sulfate, and polymyxin B sulfate) and three neuromuscular blocking agents (*d*-tubocurarine chloride (*d*-Tc), pancuronium bromide, and succinylcholine chloride (SCh)); and (2) to measure the antagonistic effect of neostigmine methylsulfate and that of 4-aminopyridine hydrochloride (4-APYR), a new type of antagonist of nondepolarizing neuromuscular blocking agents,[12, 13] on the various antibiotic-relaxant combinations.

Material and Methods

The experiments were performed on the phrenic nerve-hemidiaphragm preparation[14] of male Sprague-Dawley rats of 250 to 350 g body weight. The animals were lightly anesthetized with ether and decapitated, and the hemidiaphragms, with the phrenic nerves attached, were dissected. The costal end of the hemidiaphragm was mounted on hooks protruding from a light metal frame. The metal frame was fixed at the bottom of the organ bath (see Fig 1). The tendon of the hemidiaphragm was attached by means of another thread to a Grass model FT03C transducer. The double walled organ bath had a capacity of 60 to 70 ml and was filled with mammalian Kreb's solution (NaCl 113.0; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4$ 1.2; $NaHCO_3$ 25.0; KH_2PO_4 2.5; and glucose 11.5 mM). The bath was aerated with a 95% O_2-5% CO_2 gas mixture, its pH was 7.35 to 7.45, and its temperature was kept at 37 C by circulating water between the walls of the organ bath from a thermostatically controlled reservoir. Solutions of the compounds to be tested were added directly to the bath in increments not exceeding a total volume of 1.0 ml. The bathing solution was changed by allowing it to escape through a rubber tube attached to the outflow of the bath. Fresh Krebs' solution of 37 C was dispensed from a double walled container, the temperature of which was also thermostatically controlled. The fluid in the dispenser was also continuously perfused with a 95% O_2-5% CO_2 mixture.

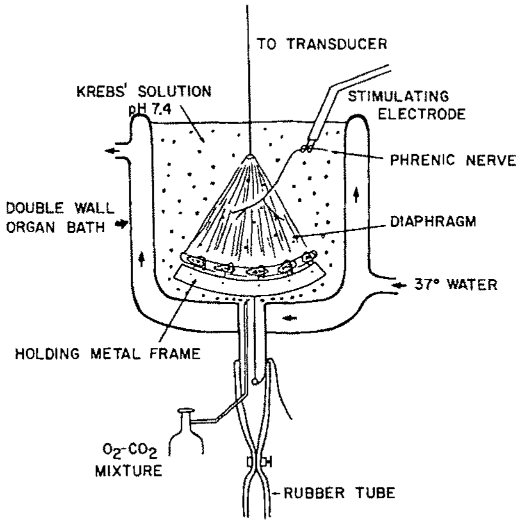

FIG 1. Schematic representation of the experimental set-up.

At the start of each experiment the twitch tensions of the indirectly stimulated hemidiaphragm preparations were determined. This was done by stimulating the phrenic nerve, which was placed on platinum electrodes immersed in the bath, supramaximally, with square wave stimuli of 0.1-msec duration at the rate of 0.1 Hz with a Grass model S48B stimulator. A resting tension of 10 g was applied to the muscle before the start of the stimulation. The indirectly elicited twitch tension was recorded on a Grass model 5A polygraph. The sensitivity of the recorder was so adjusted that 10 g of tension applied through the transducer caused a 10-mm excursion of the ink-writer. After the twitch tension became stabilized the compounds to be tested were added to the bath. All concentrations referred to in the text, tables, and figures are expressed as micrograms per milliliter of bathing fluid of the salts of the compounds added.

At first the neuromuscular effects of all compounds were determined by increasing their concentrations in the bath until twitch tensions were depressed to 2 to 10% of control values. ED_{50} values were determined from the computer (Hewlett-Packard, model 9820A)-derived dose-effect semilogarithmic regression lines. From the individual ED_{50} values the means, standard deviations (SD), and standard errors of the means (SEM) of the ED_{50} were calculated. Subsequently the antagonistic effect of 0.25 μg/ml of neostigmine methylsulfate or that of 4 μg/ml of 4-APYR, added alone or after neostigmine, were also determined. These bath concentrations of neostigmine and 4-APYR were found to be optimal in pilot experiments.

In other experiments the ED_{50} values of the antibiotics and the antagonism of the block by neostigmine or 4-APYR were determined after the addition of concentrations of neuromuscular blocking agents which alone caused no depression of the twitch. In similar experiments the ED_{50} values of neuromuscular blocking agents and the reversibility of the combined block after preliminary administration of ineffective concentrations of antibiotics were also observed

All results were expressed as percentages of control values, i.e., the twitch tensions recorded before the addition of any compounds to the Krebs' solution. The number of experiments is indicated in the tables. The data were analyzed for statistical significance by Student's *t*-test, or by paired *t*-test as applicable.

Results

Ineffective concentrations of neomycin followed by concentrations of *d*-Tc which alone were without effect, caused neuromuscular block of about 90% (Fig 2). The same was true when the order of addition of neomycin and *d*-Tc was reversed. The neuromuscular effects of other combinations of antibiotics and neuromuscular blocking agents were similar (Figs 3 to 5). The data summarized in Table 1 indicate that the preliminary addition of apparently ineffective concentrations of *d*-Tc (0.3 μg/ml), pancuronium (0.9 μg/ml), or SCh (3.0 μg/ml) caused a highly significant ($p < 0.001$) decrease of the ED_{50} of neomycin, streptomycin, and polymyxin B. Similarly, the preliminary administration of ineffective concentrations of neo-

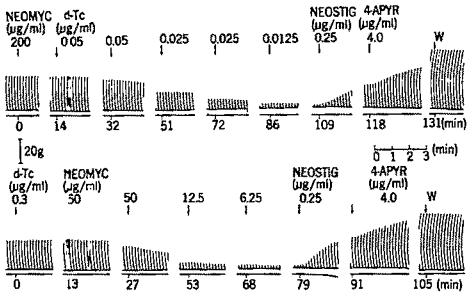

FIG 2. Mutual potentiation of the neuromuscular effects of neomycin and *d*-tubocurarine (*d*-Tc). Drugs added are expressed as micrograms per milliliter of bathing fluid. W indicates a single washout. Note that, regardless of the sequence of their administration, combinations of neomycin and *d*-Tc, which were ineffective when administered separately, caused an approximately 90% block. The block was only partially reversed by neostigmine. In contrast, 4-aminopyridine (4-APYR) increased twitch tension above its control value.

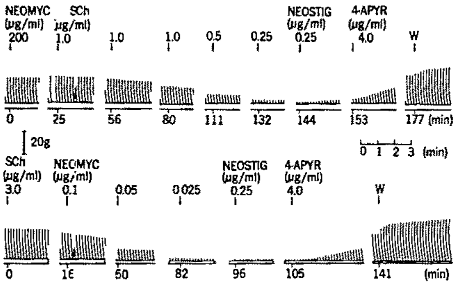

FIG 3. Mutual potentiation of the neuromuscular effects of neomycin and succinylcholine (SCh). Note that the neuromuscular block produced by these two agents was not reversed by neostigmine.

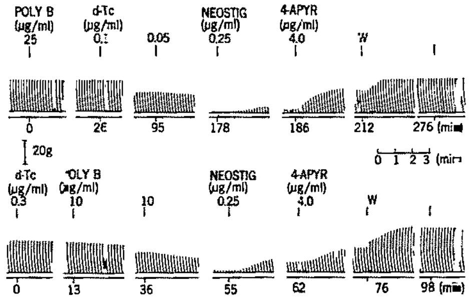

FIG 4. Mutual potentiation of the neuromuscular effects of polymyxin B and *d*-tubocurarine (*d*-Tc). Note that neostigmine caused only moderate and 4-aminopyridine (4-APYR) more marked, but still incomplete reversal of the block produced by the combined administration of these two agents.

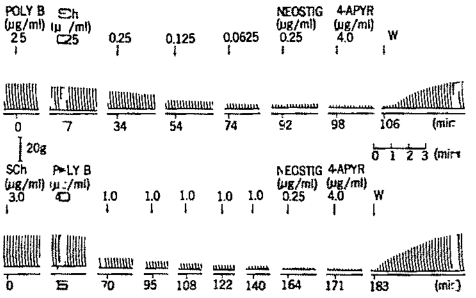

FIG 5. Mutual potentiation of the neuromuscular effects of polymyxin B and succinylcholine (SCh). Note that neither neostigmine nor 4-aminopyridine (4-APYR) was an effective antagonist of the block produced by the combined administration of these two agents.

TABLE 1

Influence of Antibiotics on the Neuromuscular Effects of Relaxants as Shown by ED_{50} Values*

Neuromuscular blocking agent	Neuromuscular blocking agent alone	Neuromuscular blocking agent preceded by		
		Neomycin (200 μg/ml)	Streptomycin (400 μg/ml)	Polymyxin B (25 μg/ml)
		μg/ml		
d-Tc	0.48 ± 0.02 (12)	0.14 ± 0.01 (4)	0.15 ± 0.01 (9)	0.13 ± 0.01 (4)
Pancuronium	2.16 ± 0.02 (11)	1.18 ± 0.03 (8)	0.53 ± 0.01 (4)	0.33 ± 0.01 (4)
SCh	7.28 ± 0.06 (12)	2.71 ± 0.13 (4)	1.36 ± 0.03 (4)	0.45 ± 0.04 (6)

* ED_{50} concentrations of the relaxants preceded by antibiotics differ significantly ($p < 0.001$) from control. Number of experiments is shown in parentheses. Values are means ± SEM.

mycin (200 μg/ml), streptomycin (400 μg/ml), or polymyxin B (25 μg/ml) significantly ($p < 0.001$) decreased the ED_{50} of neuromuscular blocking agents (Table 2).

The antagonistic effects of neostigmine or 4-APYR alone, or in combination, on the neuromuscular block caused by the different combinations of antibiotics and neuromuscular blocking agents are presented in Tables 3 to 6.

Neostigmine had little or no influence on the neuromuscular effects of the antibiotics investigated (Table 5) and only partially reversed the neuromuscular block caused by antibiotic-muscle relaxant combinations (Tables 3 and 5). In contrast, when greater than 90% block had been produced by neomycin or streptomycin, 4-APYR administered alone (Table 6) or after neostigmine (Table 5) increased the twitch tensions to values much higher than their control values. The differences between the antagonist effect of neostigmine and 4-APYR against the neomycin- and streptomycin-induced neuromuscular block are significant at the $p < 0.001$ level (Table 5). When administered alone it partially reversed (Table 6), but after neostigmine (Table 5) it had no effect on the neuromuscular block induced by polymyxin B. 4-APYR alone or preceded by neostigmine returned twitch tensions close to or above control levels after neuromuscular block produced by combinations of *d*-Tc or pancuronium with neomycin, streptomycin, or polymyxin B (Tables 3 to 6). The neuromuscular block caused by combinations of SCh with neomycin or streptomycin was also antagonized by 4-APYR (Table 4). However, when administered after neostigmine, 4-APYR was a less effective antagonist of these drug combinations (Table 3). 4-APYR alone and especially when administered after neostigmine had little effect on the neuromuscular block caused by the combined administration of SCh and polymyxin B (Tables 3 to 6). The differences between the antagonist

TABLE 2

Influence of Neuromuscular Blocking Agents on the Neuromuscular Effects of Antibiotics*

Antibiotic	Antibiotic alone	Antibiotic preceded by		
		d-TC (0.3 μg/ml)	Pancuronium (0.9 μg/ml)	SCh (3.0 μg/ml)
Neomycin	704.3 ± 13.4 (19)	70.9 ± 1.7 (4)	167.2 ± 4.6 (4)	74.6 ± 1.9 (10)
Streptomycin	849.8 ± 36.1 (22)	160.8 ± 4.2 (11)	417.5 ± 4.1 (4)	320.4 ± 8.6 (4)
Polymyxin B	110.1 ± 2.3 (9)	12.9 ± 0.6 (7)	19.7 ± 1.1 (4)	4.4 ± 0.4 (4)

* ED_{50} concentrations of the antibiotics preceded by relaxants differ significantly ($p < 0.001$) from control. Number of experiments is shown in parentheses. Values are means ± SEM.

TABLE 3

Reversal of the Neuromuscular Block Caused by Muscle Relaxants Alone or Preceded by Antibiotics, by Neostigmine Alone or Together with 4-Aminopyradine

Compound(s)	Concentration* of relaxant	Twitch tension† (% of control) after			
		Compound(s)	Compound(s) + neostigmine (0.25 μg/ml)	Compound(s) + neostigmine (0.25 μg/ml) + 4-APYR (4.0 μg/ml)	Washout
	μg/ml				
d-Tc	1.0 ± 0.05	5.6 ± 0.80	89.4 ± 9.20	122.3 ± 11.40 n.s.	122.4 ± 9.30
Neomycin + *d*-Tc	0.3 ± 0.04	8.6 ± 0.70	63.6 ± 5.80	157.4 ± 10.90	153.9 ± 10.80
Streptomycin + *d*-Tc	0.3 ± 0.01	4.7 ± 1.30	49.0 ± 4.10	144.4 ± 6.21	118.8 ± 6.02
Polymyxin B + *d*-TC	0.2 ± 0.04	4.4 ± 2.40	29.7 ± 8.40	96.8 ± 5.20	116.9 ± 3.60
Pancuronium	4.9 ± 0.30	5.9 ± 1.20	101.9 ± 4.30	156.2 ± 9.00	147.6 ± 6.60
Neomycin + pancuronium	1.9 ± 0.03	3.7 ± 1.30	79.4 ± 4.30	162.8 ± 2.30	160.1 ± 4.60
Streptomycin + pancuronium	1.2 ± 0.20	9.2 ± 2.00	76.3 ± 3.30	157.8 ± 8.50	159.5 ± 8.00
Polymyxin B + pancuronium	0.6 ± 0.04	9.7 ± 2.70	42.8 ± 5.90	110.2 ± 16.00	158.1 ± 4.70
SCH	16.0 ± 1.20	5.6 ± 0.90	2.1 ± 0.20	0	132.5 ± 7.70
Neomycin + SCh	4.6 ± 0.50	7.7 ± 2.20	12.4 ± 4.50	113.7 ± 5.00	148.2 ± 8.50
Streptomycin + SCh	3.5 ± 0.20	8.0 ± 0.20	20.3 ± 1.20	131.8 ± 16.30	141.5 ± 7.60
Polymyxin B + SCh	0.6 ± 0.04	8.2 ± 0.70	9.8 ± 1.50	7.3 ± 2.40 n.s.	108.2 ± 6.20

* Concentration of muscle relaxants (mean ± SEM of four experiments) required to depress twitch tension to <10% of control when administered alone or preceded by 200, 400, or 25 μg/ml of neomycin, streptomycin, or polymyxin B, respectively.

† Values are means ± SEM. Except when indicated (n.s.) the differences in reversal caused by neostigmine or neostigmine + 4-APYR are significant (paired *t*-test) at the $p < 0.005$ to 0.001 levels.

TABLE 4

Reversal by 4-Aminopyridine of the Neuromuscular Block Caused by Muscle Relaxants Alone or Preceded by Antibiotics

Compound(s)	Concentration* of relaxant	Twitch tension† (% of control) after		
		Compound(s)	Compound(s) + 4-APYR (4.0 μg/ml)	Washout
	μg/ml			
d-Tc	0.8 ± 0.10	4.4 ± 0.80	156.4 ± 5.20	149.9 ± 10.7
Neomycin + *d*-Tc	0.3 ± 0.02	7.9 ± .40	136.2 ± 5.60	136.5 ± 6.30
Streptomycin + *d*-Tc	0.4 ± 0.02	5.8 ± 0.90	137.8 ± 8.70	137.8 ± 10.90
Polymyxin B + *d*-Tc	0.3 ± 0.06	4.8 ± 2.10	93.3 ± 12.00	142.2 ± 9.20
Pancuronium	3.1 ± 0.07	5.4 ± .40	150.9 ± 13.10	128.8 ± 17.20
Neomycin + pancuronium	1.4 ± 0.10	6.6 ± 2.00	139.2 ± 18.20	131.7 ± 11.10
Streptomycin + pancuronium	0.9 ± 0.10	9.3 ± .30	154.6 ± 17.00	151.0 ± 15.40
Polymyxin B + pancuronium	0.7 ± 0.10	8.4 ± .20	140.3 ± 7.00	126.1 ± 1.60
SCh	10.8 ± 0.30	8.0 ± 0.60	50.6 ± 2.40	127.7 ± 1.10
Neomycin + SCh	5.3 ± 0.40	8.6 ± .10	124.1 ± 11.20	154.0 ± 7.70
Streptomycin + SCh	4.3 ± 0.10	7.2 ± 2.70	119.9 ± 6.10	137.7 ± 9.20
Polymyxin B + SCh	1.2 ± 0.08	8.9 ± .40	31.8 ± 7.10	150.3 ± 8.7

* Concentration of muscle relaxants (mean ± SEM of four experiments) required to depress twitch tension to <10% of control alone or preceded by 200, 400, or 25 μg/ml of neomycin, streptomycin, and polymyxin B, respectively.

† Values are means ± SEM.

TABLE 5

Reversal of the Neuromuscular Block Caused by Antibiotics Alone or Preceded by Muscle Relaxants, by Neostigmine Alone or Together with 4-Aminopyridine

Compound(s)	Concentration* of antibiotic	Twitch tension† (% of control) after			
		Compound(s)	Compound(s) + neostigmine (0.25 μg/ml)	Compound(s) + neostigmine (0.25 μg/ml) + 4-APYR (4.0 μg/ml)	Washout
	μg/ml				
Neomycin	1075.0 ± 25.0	8.0 ± 0.8	15.3 ± 1.2	146.8 ± 10.1	148.9 ± 8.4
d-Tc + neomycin	287.5 ± 23.9	8.2 ± 0.6	59.7 ± 5.1	141.7 ± 10.3	141.9 ± 10.2
Pancuronium + neomycin	237.5 ± 22.2	11.0 ± 1.5	46.5 ± 1.7	141.7 ± 18.6	116.3 ± 4.0
SCh + neomycin	162.5 ± 16.1	6.0 ± 0.4	14.3 ± 2.0	92.3 ± 5.6	134.4 ± 8.1
Streptomycin	1775.0 ± 14.4	6.4 ± 1.4	15.4 ± 2.8	129.4 ± 6.6	128.1 ± 8.5
d-Tc + streptomycin	375.0 ± 32.3	9.4 ± 0.5	64.3 ± 5.1	136.8 ± 7.9	139.4 ± 8.7
Pancuronium + streptomycin	650.0 ± 28.9	4.2 ± 1.8	50.3 ± 3.8	156.3 ± 13.7	155.0 ± 14.4
SCh + streptomycin	531.3 ± 42.5	6.6 ± 1.6	15.6 ± 2.0	109.9 ± 9.6	147.9 ± 10.6
Polymyxin B	118.8 ± 15.7	9.0 ± 1.5	9.9 ± 2.1	3.6 ± 1.5 n.s.	125.7 ± 10.0
d-Tc + polymyxin B	20.6 ± 0.6	7.9 ± 0.5	37.4 ± 3.0	92.9 ± 3.3	126.6 ± 11.3
Pancuronium + polymyxin B	34.4 ± 5.0	5.5 ± 2.3	22.7 ± 3.1	67.4 ± 21.4 n.s.	140.9 ± 10.9
SCh + polymyxin B	10.8 ± 0.8	7.2 ± 1.4	8.9 ± 1.6	5.7 ± 1.9 n.s.	128.7 ± 4.0

* Concentration of antibiotics (mean ± SEM of four experiments) required to depress twitch tension to <10% of control alone or preceded by 0.3, 0.9, or 3.0 μg/ml of *d*-Tc, pancuronium, or SCh, respectively.

† Values are means ± SEM. Except when indicated (n.s.) the differences in reversal caused by neostigmine + 4-APYR are significant (paired *t*-test) at the $p < 0.005$ to 0.001 levels.

effect of neostigmine and 4-APYR are also significant at the $p < 0.005$ to 0.001 level against the neuromuscular block caused by combinations of neomycin and streptomycin with *d*-Tc, pancuronium, and SCh (Tables 3 and 5).

After replacement of the bathing fluid with fresh Krebs' solution, twitch tensions returned to values above their control values in all experiments.

Comparison of the data in Table 3 with those in Table 4 and the data of Table 5 with those in Table

TABLE 6

Reversal by 4-Aminopyridine of the Neuromuscular Block Caused by Antibiotics Alone or Preceded by Muscle Relaxants

Compound(s)	Concentration* of antibiotic	Twitch tension† (% of control) after		
		Compound(s)	Compound(s) + 4-APYR (4.0 μg/ml)	Washout
	μg/ml			
Neomycin	1175.0 ± 25.0	6.1 ± 0.9	151.4 ± 8.0	152.8 ± 5.9
d-Tc + neomycin	275.0 ± 15.3	8.4 ± 0.9	129.8 ± 8.0	119.4 ± 6.5
Pancuronium + neomycin	268.8 ± 30.0	12.0 ± 3.9	162.1 ± 1.6	140.9 ± 8.3
SCh + neomycin	150.0 ± 0.0	6.3 ± 0.7	121.7 ± 4.3	133.3 ± 15.2
Streptomycin	1377.0 ± 76.0	7.1 ± 0.8	138.4 ± 8.6	119.8 ± 5.3
d-Tc + streptomycin	3250.0 ± 14.4	5.8 ± 1.9	154.1 ± 9.9	130.7 ± 11.8
Pancuronium + streptomycin	612.5 ± 7.2	7.0 ± 2.2	147.4 ± 13.5	145.4 ± 10.3
SCh + streptomycin	550.0 ± 35.4	7.7 ± 0.4	138.9 ± 4.8	157.2 ± 8.5
Polymyxin B	137.5 ± 7.2	6.0 ± 1.8	82.8 ± 8.2	107.8 ± 8.1
d-Tc + polymyxin B	30.5 ± 2.1	6.3 ± 0.9	43.8 ± 16.9	142.3 ± 9.3
Pancuronium + polymyxin B	30.0 ± 2.9	7.3 ± 3.9	156.0 ± 8.4	162.0 ± 4.0
SCh + polymyxin B	10.3 ± 1.4	5.4 ± 1.4	28.3 ± 5.5	139.2 ± 8.4

* Concentrations of antibiotics (mean ± SEM of four experiments) required to depress twitch tension to <10% of control alone or preceded by 0.3, 0.9, or 3.0 μg/ml of *d*-Tc, pancuronium, or SCh, respectively.

† Values are means ± SEM.

6 indicates that, except for the SCh-polymyxin B combinations, there is no significant difference between the antagonistic effect of 4 μg/ml of 4-APYR administered alone or preceded by 0.25 μg/ml of neostigmine.

Discussion

Lüllmann and Reuter[15] have reported that the combination of ineffective concentrations of *d*-Tc and neomycin produced a partial neuromuscular block in the rat phrenic nerve-hemidiaphragm preparations. They also observed that in the presence of 10^{-7} M (0.07 μg/ml) *d*-Tc the concentrations of neomycin, streptomycin, dihydrostreptomycin, kanamycin, and polymyxin B capable of producing a 10% neuromuscular block were reduced by factors of 1.5 to 4.0. In the present study, by using higher but still ineffective concentrations of *d*-Tc, pancuronium, or SCh, the potentiation (the interaction of two compounds may be characterized as potentiation when their combined pharmacodynamic effect is greater than the sum of the effects of the individual components) of the neuromuscular effects of neomycin, streptomycin, and polymyxin B by the neuromuscular blocking agents studied was found to be even more striking both at the ED_{50} (Table 2) and ED_{90} (Tables 5 and 6) levels. Depending on the combination of antibiotics and neuromuscular blocking agents used, the ED_{50} and ED_{90} concentrations of antibiotics decreased by factors of 2.0 to 25.0 and 1.8 to 10.5, respectively. The potentiation of the neuromuscular effects of relaxants by antibiotics was of the same order of magnitude (Tables 1, 3, and 4).

This highly significant mutual potentiation of the neuromuscular effects of antibiotics and muscle relaxants is probably due to the circumstance that antibiotics influence myoneural function both pre-[7] and postsynaptically.[15] It has been demonstrated by electrophysiologic techniques that neomycin[16] and by bioassay of the stimulated ACh release in the rat's phrenic nerve-hemidiaphragm preparation that neomycin and gentamycin[7] decrease presynaptic ACh release. The depression of ACh release could be antagonized by excess Ca^{2+}.[7] According to Dretchen et al, [17] however, in the frog sciatic-gastrocnemius preparation only gentamycin decreased presynaptic ACh release during high frequency (250 Hz) stimulation, but streptomycin, neomycin, kanamycin, and polymyxin B had no such effect. Because of species variation and differences in the stimulation parameters the results of these experiments may not be comparable with the findings of other investigators.[7] More observations will be needed using various types of antibiotics and various mammalian preparations before the effects of these compounds on presynaptic ACh release can be resolved.

In addition to their presynaptic effect antibiotics also have an antidepolarizing effect on the postjunctional membrane. Thus, for example, neomycin, streptomycin, kanamycin, and polymyxin B inhibit ACh contracture of the denervated rat diaphragm[15] and kanamycin that of the frog rectus abdominus muscle.[18] Elmqvist et al[16] demonstrated that neomycin has not only a pre- but also a postsynaptic effect. It has also been observed that in considerably higher concentrations than those necessary for blocking neuromuscular transmission, neomycin also inhibits the directly elicited twitch tension (F. F. Foldes, unpublished observations).

It is known that 4-APYR antagonizes the neuromuscular block caused by the inhibition of presynaptic ACh release caused by low extracellular Ca^{2+} or high extracellular Mg^{2+} (F. F. Foldes, unpublished observations) or by botulinus toxin.[19] The finding that 4-APYR also antagonizes antibiotic-induced neuromuscular block supports the assumption that the most important neuromuscular action of antibiotics is inhibition of presynaptic ACh release. The earlier observation[7] that the neuromuscular effects of antibiotics, similar to those of Mg^{2+}, are also antagonized by excess Ca^{2+} corroborates the validity of this assumption.

In contrast to their presynaptic effect, the postsynaptic effect of Ca^{2+}, Mg^{2+}, and presumably that of antibiotics, is similar. They inhibit the depolarization of the postjunctional membrane.[20] Therefore, the high concentrations of Ca^{2+} required to antagonize the presynaptic effects of antibiotics will decrease the sensitivity of the postjunctional membrane to depolarization by ACh and thereby partially counteract their presynaptic effect. Because of this, 4-APYR, a compound that restores presynaptic ACh release without the need for high Ca^{2+} concentrations, appears to be the agent of choice for the reversal of antibiotic-induced neuromuscular block.

Consideration of the kinetics of ACh release further elucidates the reasons for the unexpectedly high degree of mutual potentiation of the neuromuscular effects of muscle relaxants and antibiotics. The margin of safety of neuromuscular transmission is high and the amount of ACh released by the nerve impulse is about 10 times higher than that necessary for the depolarization of the postjunctional membrane.[21] Because of this, up to 70% of all the cholinergic receptors may be occupied by molecules of neuromuscular blocking agents without any noticeable effect on the indirectly stimulated twitch tension.[22] Occupancy of about 90% of the receptors produces complete block of neuromuscular transmission. In other words twitch tension decreases from 100 to 0% of control while the receptor occupancy increases from 70 to 90% and any change of the receptor occupancy above 70% causes considerable neuromuscular block. When a significant percentage of the receptors are already occupied, a second compound that increases receptor occupancy to above 70% produces a demonstrable decrease of the twitch tension. The neuromuscular effects of compounds that act primarily on the postjunctional receptors will be additive. Thus, for example, the effect of 0.3 μg/ml of *d*-Tc and that of the equivalent concentration (1.5 μg/ml) of pancuronium on the rat's phrenic nerve-hemidiaphragm preparation is additive.

Compounds that inhibit presynaptic ACh release also produce demonstrable neuromuscular block when a significant proportion of the postjunctional receptors are occupied by molecules of relaxants. The reason for this is that when a high percentage of the receptors are occluded the decreased concentration of ACh released at the neuromuscular junction fails to generate endplate potential of high enough voltage, in sufficient number of endplates, for the production of maximal twitch.

If antibiotics acted only on postjunctional receptors, their neuromuscular effect would be additive to those of muscle relaxants. However, since antibiotics have both pre- and postsynaptic effects,[7, 15] they potentiate the neuromuscular effects of muscle relaxants. The high concentrations of antibiotics required to inhibit directly elicited twitch tension are unlikely to have any significance for the depression of the twitch tension during indirect stimulation.

The observation that 4-APYR is not a very effective antagonist of the neuromuscular block caused by combinations of polymyxin B and SCh is related to the fact that 4-APYR reverses polymyxin B block less well than neomycin or streptomycin block (Fig 6) and has little or no effect on the SCh-induced neuromuscular block (Fig 7).

The finding that 4-APYR is less effective as an antagonist against the polymyxin B and colistin-induced neuromuscular block than against the block produced by neomycin, streptomycin, and other aminoglycoside-type antibiotics (i.e., gentamycin, kanamycin) (F. F. Foldes, unpublished observations) suggests that the affinity of these polypeptide antibiotics to sites of ACh release may be greater than that of aminoglycosides. The possibility cannot be exluded, however, that the mechanism of the neuromuscular effects of polypeptide-type antibiotics is different from those of aminoglycosides.

It is of interest that at the end of experiments when the bathing fluid was replaced with fresh Krebs'

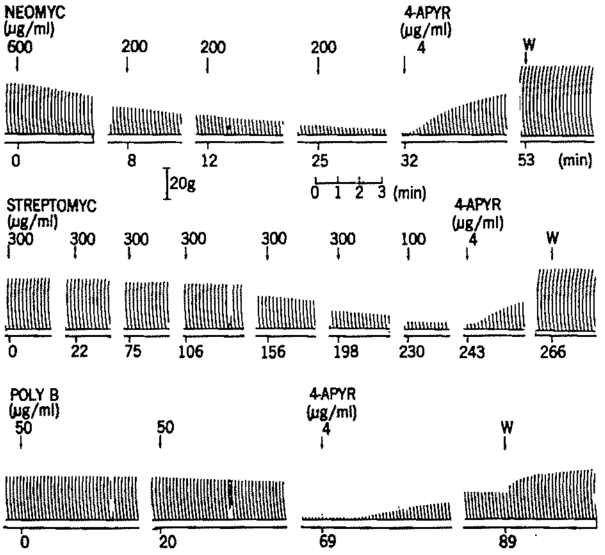

FIG 6. Comparison of the antagonist effect of 4-aminopyridine (4-APYR) on neuromuscular block induced by neomycin, streptomycin, or polymyxin B. Note that 4-APYR more effectively antagonized neomycin and streptomycin than polymyxin B.

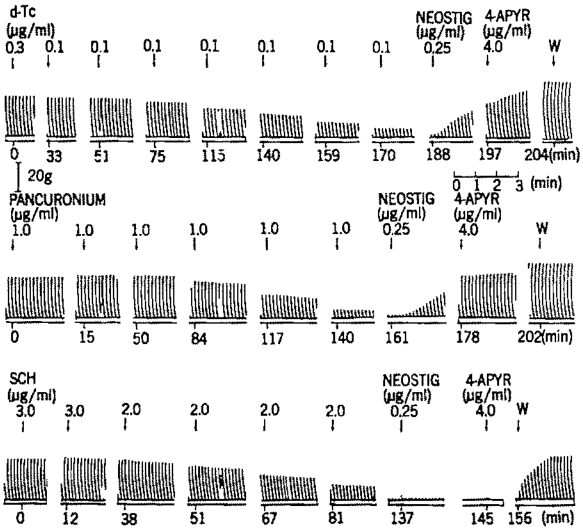

FIG 7. Comparison of the antagonist effect of neostigmine followed by 4-aminopyridine (4-APYR) on the *d*-tubocurarine (*d*-Tc)-, pancuronium-, or succinylcholine (SCh)-induced neuromuscular block. Note that neither neostigmine nor 4-APYR antagonized SCh.

solution, the twitch tensions invariably returned to levels above control value (Tables 3 to 6). This may indicate that while the antibiotics and neuromuscular blocking agents investigated dissociate readily from their receptors, 4-APYR remains fixed to its sites of action and exerts its own stimulating action on neuromuscular activity.[23]

In conclusion, it was demonstrated that the nature of the interaction of the neuromuscular effects of antibiotics and neuromuscular blocking agents represents true potentiation. This potentiation is due to the fact that antibiotics, similar to Mg^{2+} not only have a curare-like stabilizing effect[20] on the postjunctional membrane, but that they also decrease presynaptic ACh release.[7] With the exception of the neuromuscular block produced by combinations of polymyxin B and SCh, neostigmine partially and 4-APYR completely antagonized the neuromuscular block caused by the antibiotic-relaxant combinations investigated.

The degree of potentiation observed in this study facilitates the understanding of the mechanism of the neuromuscular block observed when therapeutic doses of antibiotics has been administered postoperatively to patients at times when there appeared to be no residual effects of the relaxants used during surgery.[24-26]

If and when available for clinical use, 4-APYR, which had been employed successfully in Europe for the reversal of residual nondepolarization block in surgical patients,[13] may prove to be the agent of choice for the neuromuscular block produced by combinations of antibiotics and neuromuscular blocking agents.

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Gas Exchange after Pulmonary Embolization

Gas exchange following experimental pulmonary thromboembolization was studied with an inert gas elimination technique in 17 dogs. Pulmonary arterial, systemic arterial, and expired gas concentrations of six gases infused intravenously were measured before embolization and 5, 10, 15, 30, 60, and 120 minutes after embolization. Distribution of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratios were derived from the measured concentrations. In all dogs, embolization caused an increase in blood flow and ventilation to lung areas with $\dot{V}_A/\dot{Q}$ ratios less than 1. There were no lung units with $\dot{V}_A/\dot{Q}$ ratios between 10 and 100 before embolization, but in two-thirds of the dogs, such regions developed after embolization. Ventilation to unperfused lung showed a transient increase of 2 to 6%. Radioisotope studies of lobes removed post-mortem indicated that thromboemboli rarely caused complete abolition of the lobar blood flow. Pulmonary embolization did not cause arteriovenous shunts to appear. The hypoxemia caused by embolization could be accounted for by the changes in $\dot{V}_A/\dot{Q}$ distribution. Over the 2-hour period after embolization, lung function improved as the distribution partially returned toward the preembolization patterns. *(Dantzker DR, Wagner PD, Tornabene VW, et al: Gas exchange after pulmonary thromboembolization in dogs. Circ Res 42:92-103, 1978)*

ANESTH ANALG
58:116–119, 1979

Attenuation of Blood Pressure Response to Laryngoscopy and Tracheal Intubation with Sodium Nitroprusside

Robert K. Stoelting, MD*

STOELTING, R. K.: Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. Anesth Analg 58:116–119,1979.

The time course and magnitude of change in mean arterial pressure (MAP) and heart rate (HR) following a single rapid intravenous injection of 1 μg/kg and 2 μg/kg of sodium nitroprusside (SNP) were determined in six anesthetized patients in the absence of concurrent stimulation produced by laryngoscopy or surgery. These data indicated that SNP administered 15 seconds before starting laryngoscopy would match the blood pressure lowering effects of SNP with the increase in blood pressure produced by laryngoscopy and tracheal intubation.

The change in MAP and HR during and after laryngoscopy for tracheal intubation was determined in patients receiving 1 μg/kg (10 patients) or 2 μg/kg (10 patients) of SNP 15 seconds before starting laryngoscopy. These data were compared with data for 10 patients not receiving SNP. All patients studied were scheduled for elective saphenous vein to coronary artery bypass graft operations. Immediately after tracheal intubation the maximum increase in MAP above awake levels was 18 torr ($p < 0.05$) and 13 torr ($p < 0.05$) with 1 μg/kg and 2 μg/kg of SNP, respectively, given 15 seconds before laryngoscopy whereas mean arterial pressure increased 40 torr ($p < 0.05$) after tracheal intubation in patients not given SNP. The magnitude of MAP increase was not significantly different with 1 μg/kg or 2 μg/kg of SNP ($p > 0.05$) whereas the increase without SNP was significantly greater ($p < 0.05$) than with prior SNP. SNP had no effect on the increase in HR associated with tracheal intubation.

A single rapid intravenous injection of SNP (1 to 2 μg/kg) is a practical pharmacologic method to attenuate blood pressure increases during direct laryngoscopy and tracheal intubation. Prevention of hypertension during the sequence surrounding tracheal intubation is particularly important in patients with decreased myocardial reserve or intracranial pathology.

Key Words: ANESTHETIC TECHNIQUES, Hypotensive: nitroprusside; ANESTHETIC TECHNIQUES: laryngoscopy; INTUBATION, Endotracheal: complications.

INCREASES in blood pressure and heart rate (HR) are predictable responses to direct laryngoscopy and tracheal intubation following induction of anesthesia with a barbiturate followed by succinylcholine.[1] Typically blood pressure begins to increase after about 15 seconds of laryngoscopy and becomes maximal after 30 to 45 seconds of direct laryngoscopy.[1] In this study an appropriately timed injection of sodium nitroprusside (SNP) is predicted to match the blood pressure lowering effects of this drug with the onset and duration of blood pressure elevation produced by laryngoscopy and tracheal intubation. This study describes (1) the time course and magnitude of blood

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pressure and HR changes following a single rapid intravenous injection of 1 μg/kg and 2 μg/kg of SNP during anesthesia in the absence of stimulation produced by laryngoscopy and tracheal intubation; and (2) the circulatory response to laryngoscopy and tracheal intubation with or without these doses of SNP.

Methods

The first objective of this study was to determine the time course and magnitude of mean arterial pressure (MAP) and HR changes following a single rapid intravenous injection of SNP during anesthesia but in the absence of stimulation produced by tracheal intubation. Six patients anesthetized with nitrous oxide-diazepam-morphine for elective saphenous vein to coronary artery bypass graft operations were studied. Each patient received 1 μg/kg and 2 μg/kg of SNP as a singe rapid intravenous injection in a random order with at least 10 minutes separating each dose. All measurements were completed before surgical skin incision. MAP was continuously recorded from a radial artery catheter for 1 minute before (control) and 5 minutes after SNP. HR was calculated from a 15-second portion of lead 2 of the electrocardiogram. Ventilation was controlled to maintain Pa_{CO_2} 30 to 35 torr.

The second objective was to determine the effect of prior SNP on the circulatory responses to laryngoscopy and tracheal intubation. Based on the previously determined time course of MAP change following SNP it was predicted that SNP administered 15 seconds before beginning laryngoscopy would match the blood pressure lowering effects of this drug with the blood pressure elevating effects produced by laryngoscopy for tracheal intubation. The net effect should be an attenuated circulatory response during the tracheal intubation sequence. This hypothesis was tested by measuring the MAP and HR responses to direct laryngoscopy and tracheal intubation with or without a single rapid intravenous injection of SNP preceding the onset of laryngoscopy by 15 seconds. Thirty adult patients scheduled for elective saphenous vein to coronary artery bypass graft operations were studied. No patient had received propranolol in the 24 hours prior to operation. Preanesthetic medication consisted of intramuscular morphine (8 to 15 mg) and scopolamine (0.4 to 0.6 mg) 60 to 90 minutes before anticipated time of induction of anesthesia. Upon arrival in the operating room a radial arterial catheter was placed for continuous monitoring of MAP. HR was calculated from a 15-second portion of lead 2 of the electrocardiogram. While breathing oxygen induction of anesthesia was achieved using *d*-tubocurarine, 50 μg/kg, followed 3 minutes later by thiamylal, 4 mg/kg, and succinylcholine, 2 mg/kg. Ventilation was controlled with oxygen within 15 seconds following thiamylal-succinylcholine. One minute after thiamylal-succinylcholine direct laryngoscopy for tracheal intubation was performed. Laryngotracheal lidocaine (4%, 2 mg/kg) was administered immediately prior to placement of the tracheal tube. In random order, 1 μg/kg of SNP (10 patients) or 2 μg/kg of SNP (10 patients) was rapidly injected via a peripheral intravenous catheter 15 seconds (45 seconds after thiamylal-succinylcholine) before starting direct laryngoscopy. The remaining 10 patients did not receive SNP and were considered the control group. Following tracheal intubation, ventilation was controlled with oxygen for 3 minutes after thiamylal-succinylcholine.

Data were analyzed by Student's *t*-test for paired data and analysis of variance. MAP and HR during and after intubation were compared with control measurements within the same study group as well as with corresponding measurements between study groups (i.e. no SNP, 1 μg/kg of SNP, 2 μg/kg of SNP); $p < 0.05$ was condidered statistically significant. This study was approved by the Indiana University School of Medicine Clinical Research Committee.

Results

The time course and magnitude of MAP and HR changes following a single rapid intravenous injection of SNP (1 μg/kg and 2 μg/kg) in the absence of stimulation produced by tracheal intubation or surgery are summarized in the Table. The magnitude of decrease in blood pressure after SNP was dose related whereas onset and duration of blood pressure changes were not influenced by the SNP dose. Blood pressure began to decrease 15 to 30 seconds after both 1 μg/kg and 2 μg/kg of SNP and was maximal after 45 to 60 seconds, with return toward control apparent by 90 seconds and complete after 3 to 5 minutes (Fig 1). HR did not change significantly after either dose of SNP.

MAP and HR changes during and after tracheal intubation with or without SNP (1 or 2 μg/kg) administered as a single rapid intravenous injection 15 seconds before starting laryngoscopy are sumarized in Figs 2 and 3. Decreases in MAP 1 minute after thiamylal-succinylcholine were similar with or without prior SNP (Fig 2). Direct laryngoscopy for tracheal

TABLE

Mean Arterial Pressure (MAP) and Heart Rate (HR) Before and After Sodium Nitroprusside (SNP) Injection during Anesthesia but in the Absence of Concurrent Laryngoscopy and Tracheal Intubation

Responses	Control*	Minutes after sodium nitroprusside								SNP (μg)
		0.25	0.5	0.75	1	1.5	2	3	5	
MAP (torr)										
1 μg/kg of SNP	125 ± 5	123 ± 4	111 ± 3†	100 ± 3†	98 ± 2†	103 ± 2†	109 ± 4†	116 ± 5	125 ± 4	80 ± 4
2 μg/kg of SNP	126 ± 4	124 ± 4	102 ± 5†‡	91 ± 3†‡	90 ± 3†‡	95 ± 4†	103 ± 3†	120 ± 4	128 ± 3	160 ± 8
HR (beats/min)										
1 μg/kg of SNP	95 ± 6				102 ± 3		101 ± 4	99 ± 3	95 ± 4	
2 μg/kg of SNP	94 ± 6				104 ± 4		102 ± 3	98 ± 2	95 ± 3	

* MAP and HR during anesthesia and immediately before SNP injection.
† $p < 0.05$ vs control.
‡ $p < 0.05$ for 1 μg/kg vs 2 μg/kg.

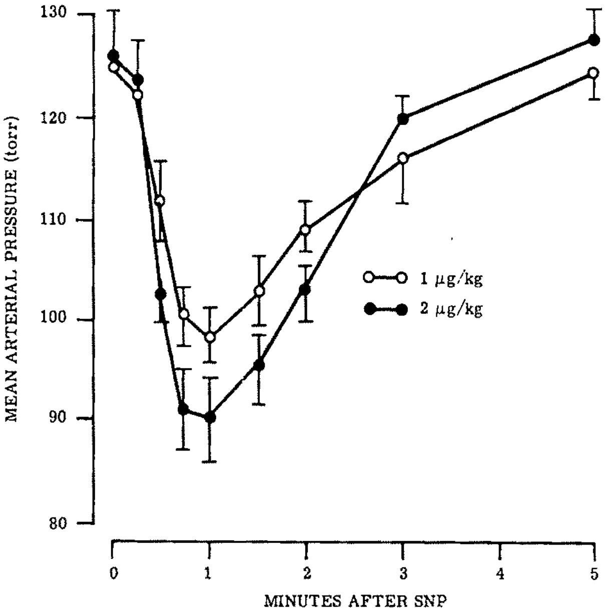

FIG 1. Changes in mean arterial pressure (means ± SE) following a single rapid intravenous injection of 1 μg/kg and 2 μg/kg of sodium nitroprusside (SNP) to six patients during nitrous oxide-diazepam-morphine anesthesia without concomitant laryngoscopy and intubation.

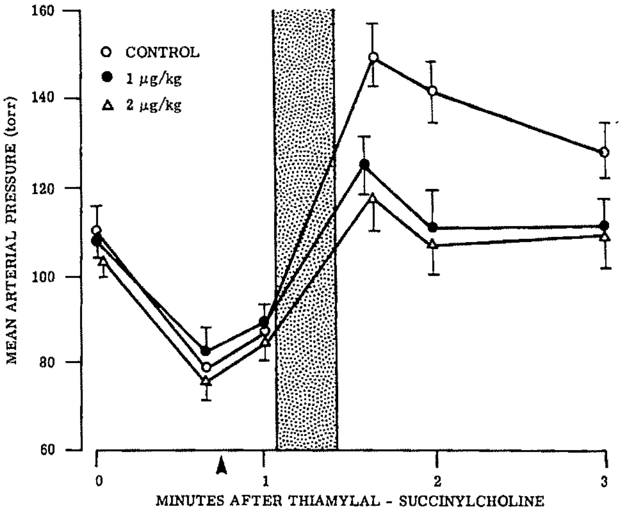

FIG 2. Changes in mean arterial pressure (means ± SE) after thiamylal-succinylcholine and in response to direct laryngoscopy and tracheal intubation with or without prior sodium nitroprusside (SNP). SNP (1 or 2 μg/kg) was administered 15 seconds before starting laryngoscopy (i.e. 45 seconds after thiamylal-succinlycholine). Arrowhead denotes SNP injection and the dotted area represents the duration of laryngoscopy for tracheal intubation.

intubation required 20 to 30 seconds. Administration of 1 μg/kg (78 ± 3 μg, mean ± SE) or 2 μg/kg (152 ± 8 μg) of SNP 15 seconds before beginning laryngoscopy significantly ($p < 0.05$) reduced the blood pressure response to laryngoscopy and tracheal intubation below that observed in patients who did not receive SNP (Fig 2). For example, compared with the awake blood pressure just before thiamylal-succinylcholine injection, the MAP increased 40 torr following tracheal intubation without prior SNP compared with 18 and 13 torr when 1 μg/kg and 2 μg/kg of SNP, respectively, preceded the start of laryngoscopy by 15 seconds. The difference in maximal MAP increase with 1 or 2 μg/kg SNP was not significant. MAP did not differ significantly from awake blood pressure 2 and 3 minutes after thiamylal-succinylcholine plus SNP and tracheal intubation but remained elevated ($p < 0.05$) at these times in the group not receiving SNP. Compared with the awake value, increases in HR were similar ($p < 0.05$) with or without SNP except 3 minutes after thiamylal-succinylcholine when HR was greater ($p < 0.05$) in patients receiving 2 μg/kg of SNP than in control patients or in those receiving 1 μg/kg of SNP (Fig 3).

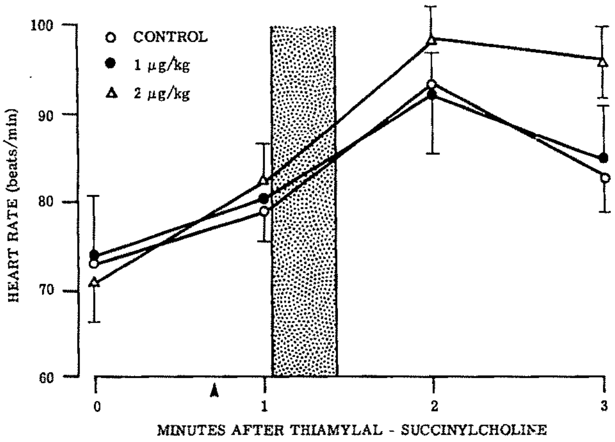

FIG 3. Changes in heart rate (means ± SE) after thiamylal-succinylcholine and in response to direct laryngoscopy and tracheal intubation with or without prior sodium nitroprusside (SNP). SNP (1 or 2 μg/kg) was administered 15 seconds before starting laryngoscopy for tracheal intubation. Arrowhead denotes SNP injection and the dotted area represents the duration of laryngoscopy for tracheal intubation.

Discussion

Blood pressure elevations during direct laryngoscopy for tracheal intubation become manifest after 15 seconds and reach peak effects if laryngoscopy is continued for 30 to 45 seconds.[1] Intravenous SNP, 1 or 2 μg/kg, administered rapidly as a single injection begins to lower blood pressure after 15 to 30 seconds with maximum decreases present after 45 to 60 seconds. Therefore, administration of SNP about 15 seconds before tracheal intubation matches the onset and maximal blood pressure lowering effects of this drug to the onset and maximal blood pressure-elevating effects produced by direct laryngoscopy and tracheal intubation. These data demonstrate that 1 or 2 μg/kg of SNP administered as a single rapid intravenous injection 15 seconds before beginning laryngoscopy attenuate to a similar degree the pressor response to tracheal intubation.

Heart rate also increases during tracheal intubation. In contrast to the predictable effects of SNP on blood pressure, it seemed unlikely that SNP would prevent HR elevations in response to tracheal intubation. Indeed, prior administration of SNP did not alter the magnitude of HR increase in response to tracheal intubation as compared with control patients except 3 minutes after thiamylal-succinylcholine (i.e. about 90 seconds after tracheal intubation). At this time HR in the group receiving 2 μg/kg of SNP was greater ($p < 0.05$) than in the control group or in patients receiving 1 μg/kg of SNP. A direct effect of 2 μg/kg of SNP on HR is questionable since the same dose administered in the absence of tracheal intubation did not alter HR. The response of HR to intubation is also not attenuated by prior oropharyngeal topical anesthesia,[1] by intravenous lidocaine,[1] or by deep inhalation anesthesia.[2]

Blood pressure and HR responses to tracheal intubation are minimal when direct laryngoscopy is brief (less than 15 seconds) and when laryngotracheal lidocaine is injected just before placement of the tracheal tube.[3] However, when a rapid laryngoscopy cannot be assured or when a high risk patient is involved (coronary artery disease, intracranial hypertension, intracranial aneurysm) it would seem prudent to attenuate pharmacologically the likely elevation of blood pressure associated with laryngoscopy and intubation. The present data confirm that a small dose of SNP (1 to 2 μg/kg) administered as a single rapid intravenous injection shortly before starting laryngoscopy significantly attenuates the pressure response to tracheal intubation. Intravenous lidocaine or topical oropharyngeal anesthesia with viscous lidocaine have also been shown to attenuate blood pressure increases during laryngoscopy.[1] However, intravenous SNP (1 to 2 μg/kg) seems preferable as it is more practical than viscous lidocaine and lacks the risk of systemic toxicity associated with intravenous lidocaine.

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58:120-123, 1979

Intrabiliary Pressure Changes Produced by Narcotic Drugs and Inhalation Anesthetics in Guinea Pigs

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ARGUELLES, J. E., FRANATOVIC, Y., ROMO-SALAS, F., AND ALDRETE, J. A.: Intrabiliary pressure changes produced by narcotic drugs and inhalation anesthetics in guinea pigs. Anesth Analg 58:120-123, 1979.

The effects of narcotic analgesic agents and two inhalation anesthetics on intrabiliary pressure (IBP) were measured before and after morphine (0.2 mg/kg), meperidine (2 mg/kg), fentanyl (0.002 mg/kg), or pentazocine (1 mg/kg) given intramuscularly to guinea pigs, and after halothane (0.5, 1.0, 1.5, or 2.0 MAC) or enflurane (same range of MAC) administered by inhalation. All narcotics except pentazocine significantly increase IBP, the increases ranging from 85.7% for meperidine to 143.4% for fentanyl. Pentazocine had no effect on IBP. Peak IBP increases occurred between 9 and 18 minutes after administration. The elevation of IBP produced by narcotics was reversed by atropine (0.05 mg/kg). No statistically significant alterations of IBP were noted during halothane or enflurane anesthesia.

Key Words: LIVER: biliary tract; ANALGESICS, Narcotic: biliary tract; ANESTHETICS, Volatile: halothane; ANESTHETICS, Volatile: enflurane.

BECAUSE of possible hepatic injury, halogenated anesthetics have been regarded by some as relatively contraindicated in hepatobiliary surgery. This has promoted the use of intravenous narcotic analgesics as anesthetics for these operations.

Abnormalities encountered in the operative cholangiogram during Innovar anesthesia have been reported as leading to unnecessary common duct explorations, accidental injuries to the sphincter of Oddi, prolonging operating time, and sphincterectomies.[1, 2]

For comparison, we have studied the effects of several narcotics and those of halothane and enflurane on the sphincter of Oddi in guinea pigs, a species with a well-developed and sensitive muscular sphincter at the entrance of the bile duct into the duodenum and an animal which in addition does not concentrate bile, thus making flow the important factor in determining intraluminal pressure.[3] Similarly, the effect of atropine sulfate on the pharmacologically elevated IBP was noted.

Methods

Narcotic Drugs

Initially, four groups of seven male guinea pigs, each weighing between 500 and 800 gm, were anesthetized with methoxyflurane. A small incision was then made in the midline of the upper abdomen and the gallbladder and common bile duct were dissected

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free. An 18-gauge polyethylene catheter, filled with saline, was introduced through the gallbladder into the common bile duct and connected to a strain gauge attached to an Electronics for Medicine monitor with a continuous recorder and oscilloscope.

After control measurements were made, animals in the first group were given morphine sulfate, 0.2 mg/kg, IM, and changes in intrabiliary pressure (IBP) were recorded every 5 minutes for 30 minutes. Animals in the second, third, and fourth groups were given meperidine, 2.0 mg/kg, IM; fentanyl, 0.002 mg/kg, IM, and pentazocine, 1.0 mg/kg, IM, respectively, IBP changes being recorded in the same fashion. Whenever IBP rose more than 50% from control, atropine, 0.05 mg/kg, was injected intramuscularly 30 minutes after the initial rise, IBP being recorded 5 and 10 minutes later. In four other groups of guinea pigs, atropine was omitted in order to allow observation of the unaltered effect of the narcotic drugs on IBP.

Inhalation Anesthetics

Nine groups of 10 adult female guinea pigs (500 to 700 gm) each were studied. Fasting animals were anesthetized with 50 mg/kg of sodium pentobarbital intraperitoneally; after restraints were applied, a surgical procedure similar to that described above was performed to cannulate the common bile duct. Tracheostomy was then performed and the trachea was cannulated with a 2.0-mm ID tube connected to a small animal Harvard pump respirator using air.

Four animals in group 5 received no anesthesia or narcotic and served as the control group for all experiments, IBP being measured every 5 minutes for 30 minutes. After obtaining control IBP measurements, animals in groups 6 to 9 received 0.5, 1.0, 1.5, and 2.0 MAC, respectively, of halothane from a Copper Kettle vaporizer previously calibrated with the aid of a mass spectometer, using a nonrebreathing system. Animals in groups 10 to 13 received enflurane at 0.5, 1.0, 1.5, and 2.0 MAC concentrations, respectively. IBP was recorded every 5 minutes for 50 minutes after initiation of the anesthetic. (MAC for halothane in guinea pigs was 1.3% and 2.6% for enflurane as determined with a Chemetron mass spectrometer (J. E. Arguelles, Y. Franatovic, F. Romo-Salas, and J. A. Aldrete, unpublished data).) Since there was no rise of IBP, atropine was not given to these two groups of animals.

The animals' temperatures were kept constant with a warming blanket. The electrocardiogram and heart rate were monitored continuously.

Results

Narcotic Drugs

All narcotic analgesics (except pentazocine) significantly increased IBP (Fig 1). The peak increase took place between 9 and 18 minutes after injection, with the IBP remaining elevated until atropine was given, except in the animals receiving meperidine. Meperidine was associated with a slight decrease 5 minutes after the peak effect had been reached. The specific peak values, as expressed in percent of the control measurements, the time of occurrence, and the mean changes observed after atropine and their statistical significance as obtained by Student's *t*-test are presented in the Table. The course and duration of IBP elevation observed in four other groups of animals, in whom atropine was omitted, are indicated by the dashed lines in Fig 1.

Atropine when given at 30 minutes after injection of narcotics decreased the elevated IBP to near control levels.

Inhalation Anesthetics

Changes of intrabiliary pressure produced by the various concentrations of halothane (groups 6 to 9) and their relation to the control levels are shown in Fig 2. The changes, although minimal and not statistically significant, suggest a dose/concentration-response during the first 25 minutes. Alterations of IBP observed in the animals that received enflurane at various concentrations are shown in Fig 3. Again, there was a decline of values from the control measurements initially obtained for each group; however, no pattern suggesting a dose relationship was observed.

Analysis of the results by Student's *t*-test revealed no statistically significant changes in IBP either between experimental values and control values, or from the changes found in the animals in the control group (group 5), with either enflurane or halothane.

Discussion

The present study confirms, in experimental animals, the abnormally high intrabiliary pressures which have been reported[1, 2, 4, 5] in patients during neuroleptanalgesia and which apparently have led to negative explorations of the biliary tract and unnecessary explorations and prolonged operating time. Other observations made in man have reported IBP elevations with morphine, meperidine, and pentazo-

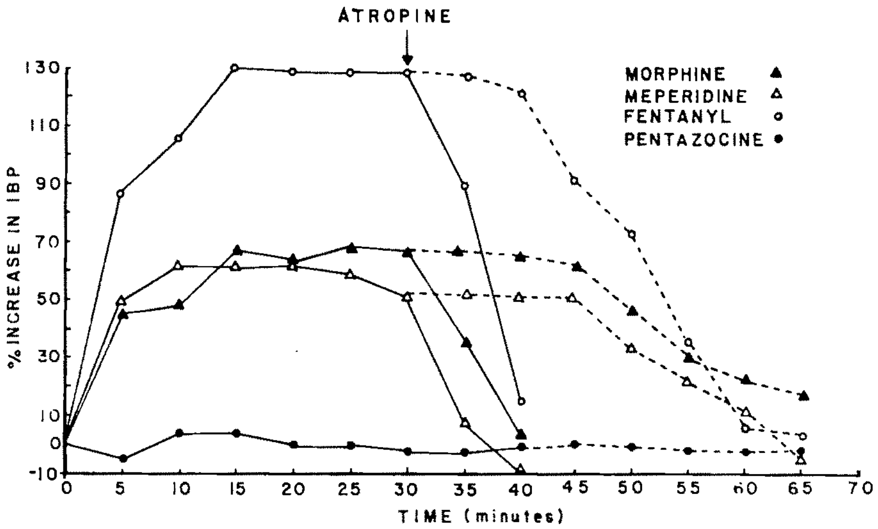

FIG 1. Percent change in intrabiliary pressure produced by administration of 0.2 mg/kg of morphine ($p < 0.05$), 2 mg/kg of meperidine ($p < 0.05$), 0.002 mg/kg of fentanyl ($p < 0.01$), and 1 mg/kg of pentazocine. Atropine (0.05 mg/kg) given 30 minutes after the narcotic reduced the elevation of IBP. The dashed lines depict the duration of IBP elevation in the groups of guinea pigs that did not receive atropine.

TABLE
Time and Degree of IBP Changes with Narcotic Drugs

Narcotic drug	Mean increase from control*	Difference from control values	Time of peak action	Mean decrease after atropine*
mg/kg, IM	%		*min*	%
Control group	0.7 ± 0.51	NS		
Morphine	94.3 ± 2.25	$p < 0.01$	18.0	38.6 ± 0.14
Meperidine (2.0)	85.7 ± 1.87	$p < 0.01$	9.0	42.1 ± 0.42
Fentanyl (0.002)	143.4 ± 28.0	$p < 0.001$	15.0	46.0 ± 0.77
Pentazocine (1.0)	4.6 ± 3.9	NS	10.0	

* Values are percentages ± standard error of the mean.

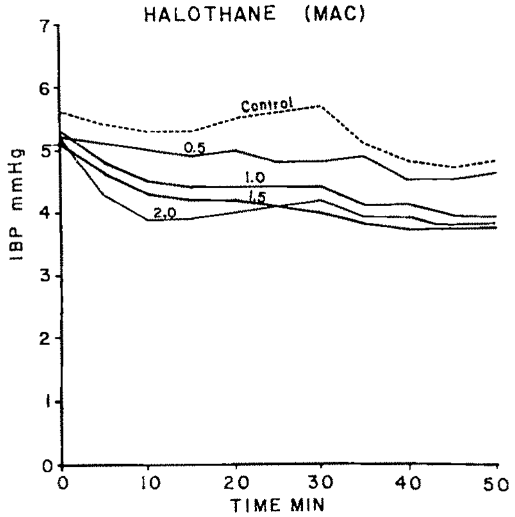

FIG 2. Halothane at different MAC levels produced slight but statistically insignificant decreases in IBP (expressed in millimeters of mercury) from control levels with a suggestion of a dose/concentration-response. The values obtained in a group of guinea pigs anesthetized with sodium pentobarbital alone (control) is shown for comparison.

cine,[4] without objective measurements of Oddi's sphincter's action. Although this report indicates that the effect of pentazocine was slight, other authors[6-8] have noted that pentazocine may occasionally produce spasms of the sphincter in patients with hepatobiliary disease. Nevertheless these latter observations lack consistency and objective measurements.

The study herein reported also confirms that fentanyl, morphine, and meperidine produce significant increases of IBP in the guinea pig, laboratory animal with a biliary tract similar to that of man.[3]

In man, fentanyl too has shown to produce spasm of the sphincter of Oddi, and to increase biliary pressure up to as much as 188% over control levels for as long as 24 minutes.[9] In our study, fentanyl was the drug producing the highest IBP increases, by far.

The increases in IBP associated with narcotics in the present studies were reversed to near control values by atropine.

Neither halothane nor enflurane produced changes in IBP from the control levels.

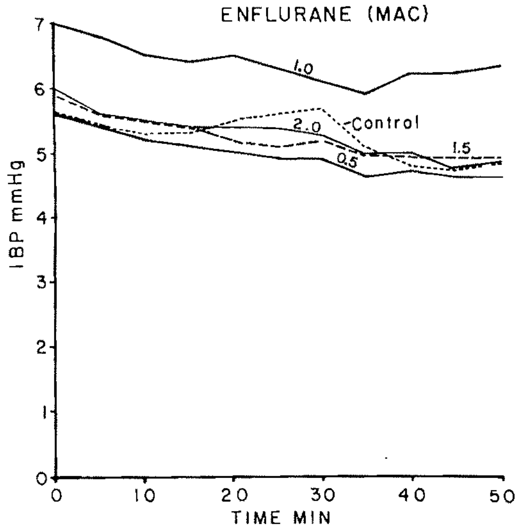

FIG 3. Alterations of IBP noted with different MAC levels of enflurane, expressed in millimeters of mercury and compared with a control group of guinea pigs.

Clinical implications derived from this study would be speculative; however, it is recommended that biliary tract dilation noted during operative cholangiograms when narcotics have been administered should be interpreted with caution in the absence of evident common duct lithiasis. When patients have received narcotics, atropine may antagonize their effects on IBP. On the other hand, neither halothane nor enflurane appear to have any significant effect on IBP; therefore either of them may be alternatively used as anesthetic, when spasm of the sphincter of Oddi is suspected during narcotic administration. Recently McCammon et al[5] used naloxone to reverse increased IBP during neuroleptanalgesia. However, since reversal of analgesia may occur, steps must be taken to prevent awareness during anesthesia when naloxone is used for this purpose.

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Diazepam and Lorazepam Premedication

Diazepam (10 and 20 mg) and lorazepam (2 and 4 mg) were studied as intravenous surgical premedicants in 120 patients. The double blind, randomized study evaluated relief of anxiety, sedation, patient acceptance, lack of recall, and side effects. Both diazepam and lorazepam proved to be excellent surgical premedicants. The basic difference between the two drugs was temporal. Both agents produced similar relief of anxiety, sedation, patient acceptance, and lack of recall. The clinical effects of intravenous diazepam peaked in 2 to 3 minutes and diminished thereafter. Lorazepam had a latent period of 8 to 15 minutes, with increasing effects at 15 to 30 minutes. Diazepam is viewed as preferable in situations where a short duration of action is required. *(Conner JT, Katz RL, Bellville JW, et al: Diazepam and lorazepam for intravenous surgical premedication. J Clin Pharmacol 18:285–292, 1978)*

SPECIAL
article

New Concepts in the Diagnosis and Fluid Treatment of Circulatory Shock

Thirteenth Annual Becton, Dickinson and Company Oscar Schwidetsky Memorial Lecture

Max H. Weil, MD, PhD., and Robert J. Henning, MD

SHOCK is a clinical syndrome characterized by protracted prostration, pallor, coldness and moistness of the skin, collapse of the superficial veins, alterations in mental status, and suppression of the formation of urine.[1] The systolic arterial pressure is usually less than 90 mm Hg or has declined more than 50 mm Hg from the basal level and the urine flow is less than 20 ml/hour. The urine is typically iso-osmolar. The ratio between urine osmolality and plasma osmolality, which reflects the tubular concentrating function of the nephron, is characteristically less than 1.5. The basic mechanism underlying all forms of acute circulatory shock is reduction of effective blood flow and inadequate tissue perfusion with decreased delivery of oxygen to the capillary exchange bed.[2] The clinical signs of shock reflect primary perfusion failure. Reduction in peripheral blood flow accounts for cold, cyanotic extremities; reduction in cerebral blood flow for altered mental alertness; reduction in renal perfusion for diminution in both the quantity and quality of urine that is excreted; and reduction in coronary blood for compromised myocardial oxygen supply and electrocardiographic S-T and T-wave changes which are indicative of myocardial ischemia. In most instances cardiac output and consequently arterial blood pressure is reduced.

With reduction in tissue perfusion and decreased delivery of oxygen to the capillary exchange bed, oxidative metabolism is impaired. There is decreased formation of high energy phosphate bonds and an increase in the permeability of cellular membranes. The cellular sodium pump fails and sodium enters and potassium escapes from the cells. The cells swell and ultimately there is rupture of lysosomal mem-

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branes with release of lytic enzymes and autodigestion.[3]

In the absence of metabolic oxygen, the anaerobic pyruvate-lactate shunt is activated and this accounts for the production of excesses of lactic acid and intracellular acidosis. The magnitude of lactic acidosis corresponds to the severity of the oxygen deficit. Arterial blood lactate therefore provides a quantitative measure of the oxygen deficit and, in turn, of the severity of perfusion failure. In patients who present with clinical signs of perfusion failure, the concentration of lactate in arterial blood characteristically exceeds 2 mmol/L.[4,5] When lactate concentrations increase from 2 to 8 mmol/L, survival progressively decreases from approximately 90% to 10%[6] (Fig 1). Lactic acidosis, therefore, is a *sine qua non* of oxygen deficit and presently represents the best single objective measure of perfusion failure (shock).[7]

Classification of Circulatory Shock

In the new classification of circulatory shock, we recognized that deficits in tissue perfusion originate from one of four categories of hemodynamic deficits: hypovolemia, cardiac failure, defects in the distribution of blood flow, and vascular obstruction (Table 1).[2]

Hypovolemic shock accounts for the vast majority of instances of acute circulatory shock in patients who are hospitalized and it is due to a primary deficit in intravascular volume.[8] The volume of blood within the intravascular space is depleted to the extent that effective tissue perfusion cannot be maintained. Although the body can survive with 15% of the total hepatic mass, 25% of the renal mass, 30% of the red blood cell mass, and less than 50% of the pulmonary parenchyma, an acute reduction of plasma volume to less than 70% of normal threatens immediate survival.[9] Hypovolemia follows the endogenous or exogenous loss of blood, plasma and/or electrolyte fluids.

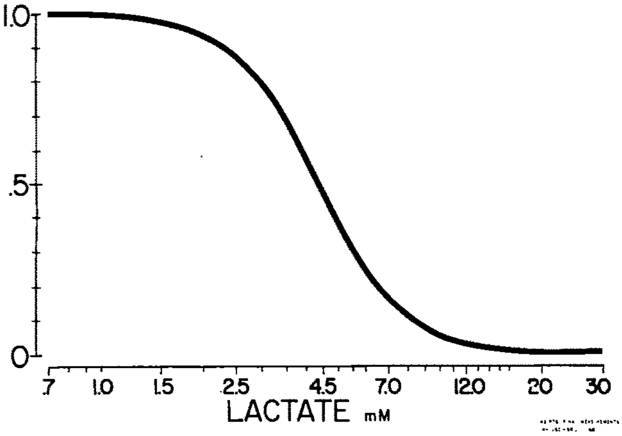

FIG 1. Statistical probability of survival in relationship to the concentration of arterial blood lactate.

TABLE 1
Reclassification of Shock States

Type of shock	Cause
Hypovolemic shock	
Exogenous	Blood loss due to hemorrhage Plasma loss due to burn, inflammation Electrolyte loss due to diarrhea, dehydration
Endogenous	Extravasation due to inflammation, trauma, application of a tourniquet, anaphylaxis, and pheochromocytoma
Cardiogenic shock	Myocardial infarction Cardiac failure Arrhythmia
Distributive shock	
High or normal resistance (increased venous capacitance selective or general)	Bacillary shock Barbiturate intoxication CNS injury Ganglionic blockade
Low resistance (arteriovenous shunt)	Inflammatory vasodilation due to pneumonia, peritonitis, abscess; reactive hyperemia
Obstructive shock (by anatomic site and mechanism	
a. Vena cava	1. Compression
b. Pericardium	2. Tamponade
c. Cardiac chambers	3. Ball-valve thrombus
d. Pulmonary circuit	4. Embolism
e. Aorta	5. Dissecting aneurysm

Cardiogenic shock represents primary pump failure. Cardiac rhythm, myocardial contractility, or myocardial work capability is compromised to the extent that cardiac output is critically reduced.

Impaired distribution of blood flow is the third category of hemodynamic defects accounting for shock. Two major subsets of distributive defects are recognized: low-resistance and high-resistance distributive defects. In the low-resistance defect, blood is either shunted from the arterial to the venous circulation[10] or transverses capillaries without effective exchange of oxygen at the cellular level.[11] This defect is commonly observed in patients with peritonitis or in the presence of one or more abscesses caused by Gram-positive pyogenic organisms. The high resistance defect is characterized by the intravascular sequestration of blood, particularly in the venous capacitance circuit and represents a selective form of relative hypovolemia.[10, 12] In such patients with "relative hypovolemia," the total intravascular volume may be normal or near normal but the capacity of the intravascular space is expanded. This is typically the case in patients with bacterial shock and/or patients who present with perfusion failure after barbiturate intoxication.[13, 14]

Finally, an impediment or obstruction to the main stream of blood flow represents an obstructive defect. This is the case in pulmonary embolism, dissecting aortic aneurysm, or pericardial tamponade. In these pathologic conditions, it is the obstruction to blood flow which precludes effective tissue perfusion and therefore accounts for the shock state.

The primary mechanism for initiating circulatory shock may be any one of these four categories of hemodynamic defects. However, the subsequent course and especially perpetuation of the shock state almost invariably involves the recruitment of other deficits. In cardiogenic shock, for instance, when there is a reduction in myocardial contractility and reduction in cardiac output, a distributive defect arises because of arteriolar constriction. At the same time, the venous return is decreased because of alterations in the venous capacitance bed. Exogenous and especially endogenous adrenergic stimulation may increase venular constriction. Consequently, capillary hydrostatic pressure is increased and this accounts for extravasation of fluid from the intravascular space into the interstitial space.[15] The intravascular volume is therefore depleted as it is in hypovolemic shock. During hypovolemic shock, reduced coronary perfusion, increased susceptibility to bacterial infection, and disseminated intravascular coagulation may perpetuate the shock state by cardiogenic, distributive, and obstructive mechanisms.

Fluid Administration

Because hypovolemia predominates as the initial cause of shock and as a complication accounting for progression of cardiogenic, distributive, or obstructive types of shock, volume replacement represents the single most important therapeutic intervention (except for cardiopulmonary resuscitation and arrest of bleeding). However, the volume that may be safely administered is contingent on the patient's cardiac competence. This is especially true in older patients. Clinical guidelines for rapid volume replacement are therefore of primary importance if acute cardiac decompensation and pulmonary edema are to be prevented. The routine measurement of the central venous pressure and the pulmonary artery and the pulmonary artery wedge pressure allows the clinician to detect limitations in cardiac competence and therefore provides an important guide for volume repletion. The pulmonary artery wedge pressure, and to a lesser extent the central venous pressure, reflect not only vascular volume but also the effectiveness with which the heart ejects the volume which is returned to it from the venous capacitance circuit. Central venous pressure measurements are useful but may be misleading in patients with significant impairment in left ventricular competence or in patients with advanced pulmonary disease. In young, previously healthy patients and in the absence of historical, physical, electrocardiographic, or radiologic signs of heart disease, the central venous pressure represents a reliable guide to volume repletion. However, in critically ill or injured patients with known cardiac or pulmonary disease who present with clinical signs of circulatory shock, the routine use of a pulmonary artery catheter is warranted.

Fluid Challenge

The response to fluid administration should be systematically assessed in patients with circulatory shock by a technique of fluid challenge. A volume of 50, 100, or 200 ml of fluid is administered over a 10-minute interval through a peripheral venous catheter.[16] Fluid challenge is also indicated in patients in whom the initial pulmonary artery diastolic or wedge pressure or central venous pressure is increased if the patient presents with clinical signs of circulatory shock. Central venous pressure and pulmonary artery wedge pressure, on occasion, may be increased rather than decreased after massive blood or fluid loss in elderly patients with limited cardiac reserve because of compromised coronary blood flow and therefore, impaired cardiac competence. If the central venous pressure (CVP) is less than 8 cm H_2O, 200 ml of fluid is administered through a peripheral vein over a 10-minute interval (Table 2). When the CVP is greater than or equal to 8 cm H_2O but less than 14 cm of H_2O, 100 ml of fluid is administered over a 10-minute interval of time. When the CVP is greater than or equal to 14 cm of H_2O, 50 ml of fluid is administered over a 10-minute period. A "5-2" rule is employed with a central venous pressure catheter during volume administration. If at any time during the infusion the CVP rises by more than 5 cm of H_2O, the infusion

TABLE 2

Guidelines for Fluid Challenge Utilizing Central Venous Pressure Monitoring

Fluid challenge: CVP, cm H_2O (5-2 rule)			
Observe CVP for 10 min	<8 cm H_2O	200 ml × 10 min	Peripheral IV
	<14 cm H_2O	100 ml × 10 min	
	≥14 cm H_2O	50 ml × 10 min	
During infusion 0–9 min	>5 cm	STOP	
Following infusion	>2 cm < 5 cm	Wait 10 min	
	>2 cm	Wait STOP	
	≤2 cm	Continue infusion	

should be discontinued. Following the infusion, if the CVP has risen by less than 5 cm but more than 2 cm of H_2O, the patient is observed for a 10-minute interval. If the CVP persistently exceeds 2 cm H_2O of the starting value, the patient is monitored but no additional fluid is administered. If it declines to within 2 cm H_2O of the starting value, the fluid challenge is resumed. In each instance, the pressure value immediately preceding the fluid challenge serves as the reference measurement. Fluid is administered until either the hemodynamic signs of shock are corrected or the central venous pressure "5-2" rule is violated.

TABLE 3

Guidelines for Fluid Challenge Utilizing Pulmonary Artery Diastolic or Pulmonary Artery Wedge Pressure Monitoring

Fluid challenge: P_{PAW}, P_{PAD} mm Hg (7-3 rule)		
Observe P_{PAD}/P_{PAW} for 10 min	<12 mm Hg	200 ml × 10 min
	<16 mm Hg	100 ml × 10 min
	≥16 mm Hg	50 ml × 10 min
During infusion 0–9 min	>7 mm Hg	STOP
Immediately following 10 min infusion	>3 < 7 mm Hg	Wait 10 min
	>3 mm Hg	Wait STOP
	≤3 mm Hg	Continue infusion

A "7-3" rule is employed when measurements of pulmonary artery diastolic (P_{PAD}) or "wedge" (P_{PAW}) pressure are available (Table 3). The P_{PAD} is a valid indication of left-sided filling pressures in the absence of pulmonary hypertension. However, when pulmonary diastolic pressure exceeds wedge pressure by more than 5 mm Hg and if changes in P_{PAW} do not closely correspond to simultaneous changes in P_{PAD}, P_{PAW} should be utilized. Measurement of P_{PAD} decreases the risk of pulmonary vascular injury and pulmonary infarction caused by prolonged inflation of the balloon of the flow-directed pulmonary artery (Swan-Ganz) catheter.[17,18] When the pulmonary artery diastolic pressure or the pulmonary artery wedge pressure is less than 12 mm Hg, 200 ml of fluid is administered over a 10-minute interval through a peripheral intravenous catheter. If the pulmonary artery diastolic pressure or the pulmonary artery wedge pressure is greater than 12 mm Hg but less than 16 mm Hg, 100 ml of fluid is administered. If the pulmonary artery diastolic pressure or the pulmonary artery wedge pressure is equal to or greater than 16 mm Hg, a 50-ml aliquot of fluid is administered. The pulmonary artery pressure is monitored during the infusion and the "7-3" rule is utilized: If the pulmonary artery diastolic or pulmonary artery wedge pressure increases by 7 mm Hg at any time during the infusion and remains at this level for more than 1 minute, the infusion is stopped. If following the 10-minute infusion, the pulmonary artery diastolic pressure or the pulmonary wedge pressure has increased by less than 7 mm Hg but more than 3 mm Hg, the patient is observed for 10 minutes. If the pulmonary pressure persistently exceeds 3 mm Hg of the starting value, the patient is monitored but fluid challenge is suspended. However, if the pulmonary pressure declines to within 3 mm Hg of the starting value, the fluid challenge is resumed. Once again, the pressure value recorded immediately preceding the most recent 10-minute interval of fluid infusion serves as the reference measurement. Fluid administration by the "7-3" rule is continued until either the hemodynamic signs of shock are reversed or the "7-3" rule is violated. When the safe limits of fluid challenge are exceeded and perfusion failure persists, a trial of therapy with inotropic drugs, such as digitalis glycosides, vasodilator (afterload reducing) agents, or mechanical circulatory assistance may be justified. If such interventions improve myocardial performance with a decline in central venous and pulmonary artery pressure, fluid challenge may then be resumed.

Selection of Fluids

During acute, massive hemorrhage both red blood cells and plasma are lost and should be replaced with whole blood or, preferably, reconstituted washed red blood cells and plasma protein solution. Four hours after acute hemorrhage, the intravascular volume is often increased by fluid transfer from the extravascular compartment into the intravascular compartment. Accordingly, hemoglobin and hematocrit concentrations are reduced. If the plasma volume has been expanded with crystalloid solutions after acute hemorrhage, red blood cells are subsequently administered. When both the hemoglobin and the protein concentration are reduced, we presently advise that both red blood cells and albumin or plasma protein fraction be administered. When plasma losses are caused by inflammatory processes such as peritonitis, or pancreatitis, or after blunt trauma to an extremity, the hemoglobin and hematocrit concentrations may be increased but the protein concentration may be decreased. Solutions of albumin or plasma protein fraction are presently utilized for fluid challenge under these conditions. Excessive losses of chloride during vomiting and selective losses of sodium in patients with diarrhea, in which electrolyte concentrations may be depleted but hematocrit and plasma concentrations are both increased, are presently managed by infusions of physiologic (0.9%) sodium chloride solutions with appropriate additions of potassium and minor cations.

Colloid Osmotic Pressure

The major risk of rapid volume expansion during circulatory shock is pulmonary edema. Our concepts of pulmonary edema have been greatly modified in the last several years by clinical investigations which have quantitated the relationships between the capillary hydrostatic pressure and the colloid osmotic (oncotic) pressure.

E. H. Starling, in 1896,[19] defined the quantitative changes in fluid flux between the capillary membrane and the interstitium, as follows:

$$F_i = K(P_c - P_i) - (\Pi_c - \Pi_i)$$

in which:

F_i = fluid pressure favoring filtration of fluid into the interstitium;
K = Membrane permeability coefficient;
P = hydrostatic pressure;
c = capillary;
i = interstitium;
Π = colloid osmotic (oncotic) pressure.

The larger the fluid pressure (F_i), the greater the likelihood of extravasation of fluid into the interstitium and *edema* formation.

Pulmonary edema may be brought about *either* by an increase in the pulmonary capillary hydrostatic pressure or by a decrease in the colloid osmotic (protein) pressure of the fluid within the capillary. A classic study by Guyton and Lindsey[20] illustrates the relationship between the colloid osmotic pressure and the capillary hydrostatic pressure. In dogs with normal plasma protein concentrations, pulmonary edema developed when the left atrial pressure or pulmonary capillary hydrostatic pressure was increased to levels exceeding 25 mm Hg. When the plasma protein concentration was reduced to approximately one-half, by dilution of plasma with physiologic salt solution, pulmonary edema developed when the left atrial pressure was elevated to levels of 11 mm Hg. With the availability of practical methods for the clinical measurement of colloid osmotic (oncotic) pressure (COP) in plasma or serum[21, 22], it is now possible to quantitate precisely this additional variable that determines the transport of fluid across the pulmonary capillary and hence the likelihood of pulmonary edema.

Normal colloid osmotic pressure of plasma is 25 mm Hg in the upright subject.[21, 22] The colloid osmotic pressure declines to 21 mm Hg in the supine individual after 4 hours of bed rest because of loss of the normal gravimetric gradient and reabsorption of hypo-oncotic fluid from the interstitial space. Pulmonary capillary pressure may be estimated from the pulmonary artery wedge (PAW) pressure. An estimate of the average pressure relationships in the pulmonary capillary is shown in Fig 2. At the arteriolar end of the pulmonary capillary in the mid-lung of the supine subject, the normal pressure is estimated to be 15 mm Hg. At the venous end of the pulmonary capillary, the estimate of hydrostatic pressure is 7 mm Hg. The lung is unique as an organ because it provides

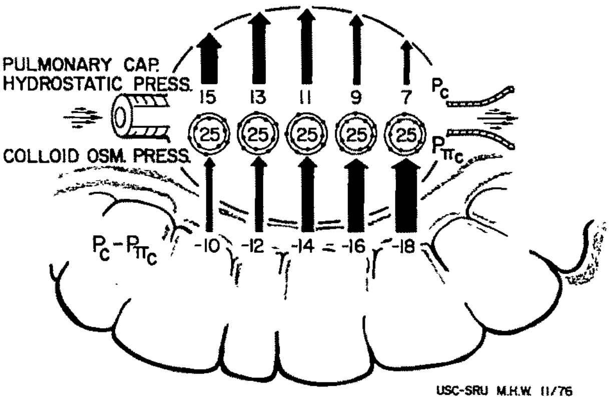

FIG 2. Normal colloid osmotic pressure-pulmonary hydrostatic pressure relationships in the central portion of the lung. Colloid osmotic-hydrostatic pressure gradient ranges from 10 mm Hg at the arteriole to 18 mm Hg at the venule.

mechanisms for maintaining its tissue spaces relatively dry in contrast to systemic tissues. The intravascular colloid osmotic-pulmonary hydrostatic pressure gradient, which, in the supine subject normally ranges from 10 to 18 mm Hg, accounts for the capability of the lung to minimize accumulation of fluid in the alveolar and interstitial spaces. As Staub and associates[23] have demonstrated, the lymphatic system of the lung also has an important role in maintaining a gradient of fluid flow by which extravascular lung water is drained into the venous system. Both the force and the rate of lymph flow are increased when fluid filtration is increased. Normally, the interstitial protein osmotic pressure is one-half or less than that of plasma colloid osmotic pressure and constitutes another important variable for maintenance of normal gradients.[24] When capillary filtration is augmented and the volume of interstitial fluid is increased, the interstitial colloid osmotic pressure is reduced. Together with increased lymphatic flow, this provides an important safety factor which decreases the risk of alveolar pulmonary edema.

When left ventricular end-diastolic pressure (left-sided filling pressure) is increased, pulmonary hydrostatic pressure is correspondingly increased. If pulmonary hydrostatic pressure exceeds the colloid osmotic pressure, there is a net gradient of outward fluid flow and, consequently, pulmonary edema (Fig 3). This is in part tempered by the simultaneous changes in lymphatic flow and interstitial colloid osmotic pressure which we have already described. When osmotic pressure is reduced following loss or dilution of plasma proteins, pulmonary edema may occur with only mild increases or even in the absence of increased left ventricular filling pressure. Decreases in colloid osmotic pressure may be due to increases in permeability of pulmonary or systemic capillaries,[25] failure of hepatic production or mobilization of plasma albumin,[26] major losses of blood or plasma due to hemorrhage or inflammation,[27-29] or to the reduction of plasma proteins by the administration of large amounts of crystalloid (non-colloid containing) fluid.[30]

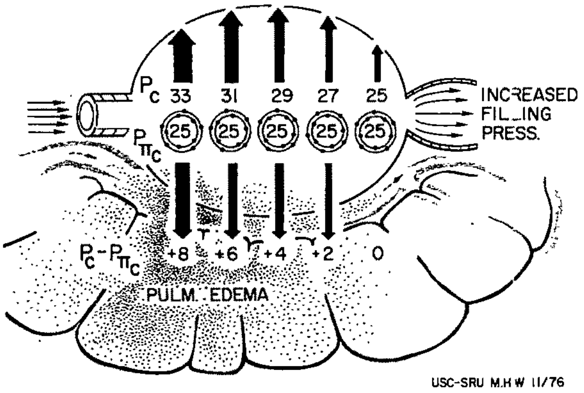

FIG 3. Colloid osmotic-hydrostatic pressure relationships during pulmonary capillary hypertension secondary to left ventricular failure. Pulmonary hydrostatic pressure exceeds colloid osmotic pressure; consequently, fluid extravasates from the intravascular space into the interstitial and alveolar spaces.

Oncotic-Hydrostatic Pressure Gradient

Our earlier studies have demonstrated very predictable relationships between the production of acute pulmonary edema and the algebraic difference between the colloid osmotic pressure and the pulmonary artery wedge pressure which we have referred to as the COP-PAW gradient.[31-33] This presumes that there is no major defect in pulmonary capillary permeability of the type observed with heroin intoxication,[34] salicylate overdose,[35] bacterial lung infection,[36] or aspiration pneumonitis.[37] Permeability pulmonary edema may be distinguished from hemodynamic (oncotic-hydrostatic) pulmonary edema by sampling endobronchial fluid.[38, 39] The COP of endobronchial fluid is typically less than 50% of plasma COP and is usually less than 60% of that of plasma in patients with hemodynamic pulmonary edema. However, it exceeds 90% of that of plasma in patients with permeability pulmonary edema.

The colloid osmotic pressure (COP) and the pulmonary artery wedge pressure should be measured simultaneously. If the colloid osmotic pressure-hydrostatic pressure difference is persistently greater than 8 mm Hg, it is unlikely that the patient will develop acute pulmonary edema. When the difference between the COP and the PAW ranges from 4 to 8 mm Hg, the risk of pulmonary edema is significantly increased. If the difference between the COP and the PAW is persistently less than 3 mm Hg for more than 12 hours, pulmonary edema is almost invariably observed (Table 4). When pulmonary edema is reversed in patients, the colloid osmotic hydrostatic pressure gradient is increased to levels of 8 mm Hg or more; in patients who fail to respond to treatment, the colloid osmotic pressure-hydrostatic pressure gradient typically remains less than 3 mm Hg.[30]

The practical implication of these new developments in the context of this presentation, relates to the prevention of acute pulmonary edema in patients during fluid repletion. The colloid osmotic pressure and the pulmonary artery wedge pressure should be

TABLE 4

Colloid-Hydrostatic Pressure Gradient Versus Roentgenographic Severity of Pulmonary Edema*

COP-PAW (mm Hg)	No. of patients	Grade of pulm. edema	Grade 2+ or greater	% Significance	p
−12 to 0.1	9	2.8+	8/9	89	<0.05
0 to 5.9	15	2.2+	8/15	53	<0.001
≥6.0	25	0.8+	5/25	20	<0.05

* Pulmonary edema was graded from the chest roentgenogram using a scale of 0 (absent) to 4+ (florid alveolar edema) for 49 patients with acute cardiorespiratory failure.

measured simultaneously when patients are resuscitated by infusion of blood, electrolytes, or crystalloid fluids. The COP-PAW gradient should be maintained at levels exceeding 7 mm Hg by either manipulating the left ventricular filling pressure or by the use of colloid-containing fluids.

Acute Cardiogenic Pulmonary Edema

Acute pulmonary edema, when caused by left ventricular failure, represents a form of acute perfusion failure (shock) characterized by metabolic acidemia, lactic acidemia, and a reduction in forward blood flow.[40] Extensive investigations of patients with acute cardiogenic pulmonary edema in our unit have revealed a reduction rather than an expansion of the intravascular blood volume in these patients.[41, 42] With the increase in the capillary hydrostatic pressure above the colloid osmotic pressure, and the production of a negative COP-PAW gradient, large quantities of fluid, which are low in protein content, extravasate from the intravascular space into the interstitial and alveolar spaces of the lung during acute heart failure. As much as one-half of the plasma volume may be lost from the intravascular spaces into the interstitial space and alveoli of the lung.[43, 44] Indeed, the volume deficit which accompanies acute pulmonary edema may occasionally be so marked that the patient may present with acute circulatory failure which is due to primary hypovolemic shock. Seven patients with ischemic heart disease with unequivocal clinical signs of acute left ventricular failure, radiographic signs of acute pulmonary edema, hypoxemia combined with respiratory and metabolic acidemia, hypovolemia, and peripheral circulatory failure with hypotension have been studied by our group.[45] Reduction in intravascular volume, documented in each case, together with reduction in ventricular filling pressures, aggravated the low cardiac output state and produced the circulatory failure (shock). Perfusion failure was promptly reversed after infusion of 5% human serum albumin in amounts ranging from 0.5 to 2.0 L *without* exacerbation of the pulmonary edema (Table 5). Responsiveness to furosemide, a potent loop diuretic, was then restored.

Hypovolemia requiring fluid repletion is an uncommon complication in patients who present with acute pulmonary edema. Nevertheless, the fact that acute circulatory failure may occasionally be reversed by volume infusion, provides important confirmation of the important role of volume depletion in patients with acute cardiogenic pulmonary edema.

Summary and Conclusion

The primary defect underlying all forms of acute circulatory failure (shock) is reduction of effective blood flow with inadequate tissue perfusion and a decrease in the delivery of oxygen to the capillary exchange bed. Lactic acid accumulates as a result of anaerobic metabolism and provides a quantitative measurement of the perfusion failure and the oxygen deficit. Hypovolemia is the most frequent cause of acute circulatory failure (shock) with lactic acidosis seen in the general hospital and is due to a primary deficit in the intravascular blood volume.

Routine measurement of the central venous pressure and/or the pulmonary artery pressure provides clinical guidelines for volume repletion in patients with acute circulatory failure and allows the clinician to detect limitations in cardiac competence prior to the development of acute pulmonary edema. Large volumes of fluid may be safely administered utilizing the "5-2" and "7-3" rules of fluid challenge.

Recent investigations in our unit have emphasized the importance not only of the pulmonary hydrostatic pressure but also the colloid osmotic pressure in the production of acute pulmonary edema. A colloid osmotic-hydrostatic pressure gradient which is persist-

TABLE 5

Reversal of Acute Perfusion Failure in Seven Patients with Acute Cardiogenic Pulmonary Edema by Infusion of Plasma Albumin

	Mean arterial pressure (mm Hg)	P_{PAW} (mm Hg)	Plasma volume (ml/kg)	Total blood volume (ml/kg)
Initial measurement	69	9.4	36.9	56.8
Post-albumin infusion	81	14.7	46.0	67.2
		$p < 0.05$	$p < 0.05$	$p < 0.05$

ently less than 3 mm Hg for 12 hours, is almost always associated with acute pulmonary edema.

Acute pulmonary edema, when caused by left ventricular failure, represents a form of acute perfusion failure (shock) with metabolic acidemia, lactic acidemia, and a reduction in forward flow. Large quantities of fluid may be lost from the intravascular space into the interstitial and the alveolar spaces during the production of acute cardiogenic pulmonary edema. Measurement of the intravascular volume demonstrates a reduction rather than an expansion of the plasma volume.

Acute pulmonary edema is not fundamentally different from other types of shock in which the shock state is initiated by one primary defect, and during the course of its progression, other mechanisms are called into action. In the instance of acute cardiogenic pulmonary edema, the primary defect is cardiac pump failure and the secondary defects include hypovolemia and distributive defects associated with expansion of the venous capacitance bed and arterial vasoconstriction. The volume deficit may occasionally be so great during acute cardiogenic pulmonary edema that fluid repletion may be required as an initial therapeutic intervention to restore effectiveness of conventional treatment of myocardial failure with diuretic agents and digitalis glycoside.

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Potency of Pancuronium and Its Metabolites

To determine the potency of pancuronium and its metabolites 3-OH-, 17-OH-, and 3,17-OH-pancuronium, cumulative dose-response curves were determined in five anesthetized patients with each drug. The ED_{50} (dose required for a 50% depression of twitch tension) was established for each drug. Pancuronium (ED_{50} = 0.041 mg/kg) was 2 times more potent than 3-OH-pancuronium (ED_{50} = 0.082 mg/kg), 50 times more potent than 17-OH-pancuronium (ED_{50} = 2.0 mg/kg), and 54 times more potent than 3,17-OH-pancuronium (ED_{50} = 2.15 mg/kg). In 21 additional patients, one equipotent dose of either pancuronium or one of its metabolites was given as an intravenous bolus. Onset time and duration of neuromuscular blockade from 3-OH- and 3,17-OH-pancuronium did not differ significantly from that of pancuronium: 17-OH-pancuronium had a shorter duration of action than did pancuronium. Although pancuronium tended to have a slightly longer elimination half-life, the pharmacokinetics of the four drugs did not differ significantly. The elimination half-lifes were 110, 68, 73, and 71 minutes for pancuronium and its 3-OH, 17-OH, and 3,17-OH derivatives, respectively. The authors conclude that although pancuronium is more potent than its 3-OH, 17-OH, and 3,17-OH metabolites, the pharmacokinetics of these three metabolites do not differ from each other and from that of pancuronium. *(Miller RD, Agoston S, Booij LHD, et al: The comparative potency and pharmacokinetics of pancuronium and its metabolites in anesthetized man. J Pharmacol Exp Ther 207:539–543, 1978)*

CLINICAL reports

Management of Hemophiliac Patients Undergoing Surgical Procedures

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The development of factor VIII (antihemophiliac globulin or AHG) concentrates and parallel advances in our understanding of the coagulation processes have greatly facilitated management of patients with clotting disorders. Elective surgery is now routinely done on the well-prepared patient with hemophilia. The contrast between the current approach and that prevailing a few year ago is illustrated in the following case report.

Case Report

In 1966 a 21-year-old man with severe hemophilia A was admitted to Colorado General Hospital because of abdominal bleeding, presumably due to a ruptured spleen. Shortly before surgery he received 3 gm of fibrinogen and two units of fresh frozen plasma (FFP). During surgery he received an additional 4 gm of fibrinogen, two units of FFP, two units of fresh whole blood, and 6 gm of epsilon-aminocaproic acid (EACA). On the night following the operation he was given additional FFP, followed by six to nine units of FFP per day for the first 10 postoperative days. During the first postoperative week he sustained spontaneous epistaxes, hemarthroses into one shoulder and into both knees, and continuous oozing into the wound site. Application of pressure dressings, ice packs, and topical thromboplastin to the incision failed to achieve complete hemostasis. The surgical wound healed slowly but the patient finally left the hospital 55 days after the operation. A final note on the chart read: "Since the patient had three units of fresh whole blood 10 days ago, he still should have enough antihemophiliac globulin on board not to be in danger of bleeding at this time."

Since 1956, increased understanding of the clotting process, of the pharmacokinetics of factors VIII and IX, and the development of factor concentrates have subsequently revolutionized medical and surgical care of the hemophiliac patient.

Methods and Materials

Because of the scarcity of clinical reports dealing with current concepts of anesthetic management of the hemophiliac,[1-4] we reviewed the hospital records of patients with this disease who required anesthesia at Colorado General Hospital from 1972 to 1977. Particular attention was given to identification and pre- and postoperative correction of the deficient factor, to problems in anesthetic management, and to events occurring in the first 5 postoperative days. The review included 21 male patients who underwent a total of 42 operative procedures.

Information recorded included coagulation studies (especially factor level determination and inhibitor screen), the amount and type of concentrate used to correct and maintain normal clotting, the anesthetic agents and techniques used, as well as the number and type of operative procedures performed.

Hemostasis was evaluated by measuring the blood collected in "Hemovacs" during the first 2 to 4 postoperative days, and by daily inspection of the wound site until the time of discharge of the patient from the hospital.

Results

Most of the patients in this study were from 20 to 40 years old, had 5% or less of factor VIII activity (only two of the 21 patients had factor IX deficiency), and were classified as A.S.A. physical class II or III. The majority (28 of 42) of surgical procedures were

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orthopedic; 19 of these were performed on an extremity, thus permitting use of an orthopedic tourniquet, which reduced operative blood loss markedly (Table 1).

Patients were given factor VIII or IX concentrate within 2 hours before being brought to the operating room. They also received another infusion of the deficient factor immediately following the operation, followed by additional infusions of factor concentrate every 8 hours for the next 3 to 5 days, then every 12 hours until discharge from the hospital. The level of deficient factor immediately before operation, as well as the patient's lowest level observed during the first 5 postoperative days, is shown in Table 2.

General anesthesia was given by mask in 29 of the 42 procedures. Endotracheal intubation was performed in 11 cases, usually 60 to 90 minutes after preoperative correction of deficient clotting factor; there were no complications associated with laryngoscopy or intubation. In two patients axillary blocks were performed without complication.

A variety of preanesthetic medications was given, though most consisted of intramuscular injections of narcotic and atropine. Even in cases in which the premedication was given before preoperative correction of deficient factor, there were no instances of muscle hematoma secondary to these injections. The anesthetic agents most frequently used were nitrous oxide with halothane, with enflurane, narcotic-relaxant, or ketamine being used occasionally.

TABLE 1
Operative Blood Loss with Various Types of Procedures

Procedure	No. of procedures	Blood loss (ml)			
		100	100–500	500–1000	1000–1500
Orthopedic (tourniquet)	19	10	9		
Orthopedic (no tourniquet)	9	5	1	2	1
Abdominal	5	4			1
Other	9	5	4		
Totals	42	24	14	2	2

TABLE 2
Corrected Level of Deficient Factor in Percentage of Normal*

Factor VIII or IX level at time of surgery	Lowest level of factors VIII or IX during first 5 postoperative days				
	1	2	3	4	5
57.0 ±19.5	30.6 ±11.6	32.5 ±11.6	30.4 ±15.3	28.5 ±12.2	29.2 ±11.3

* Values are percentage of normal ± SD.

No excessive bleeding was observed intraoperatively (Table 1). There were, however, five instances of postoperative bleeding. In two of these, inadequate factor replacement was the cause, since oozing from the surgical incision quickly stopped with administration of additional factor VIII or IX.

A third patient had a similar problem in spite of adequate levels of factor VIII and the absence of inhibitors. The factor VIII concentrate initially used was cryoprecipitate; when commercial factor VIII concentrate was substituted, hemostasis was promptly achieved.

One patient who had undergone vagotomy and pyloroplasty for peptic ulcer disease had hematemesis on the 4th postoperative day. Since high factor VIII levels were present, emergency revision of the pyloroplasty was performed, and the patient recovered uneventfully.

The fifth postoperative case of wound bleeding was in a patient being treated with indomethacin; upon withdrawal of the drug the oozing promptly disappeared.

Discussion

Analysis of this series reveals that the typical hemophiliac undergoing surgery is a man from 20 to 40 years old, in fairly good health except for his hematologic disorder, and scheduled to have an orthopedic procedure on an extremity using a tourniquet.

In our series, the corrected levels of the deficient factor pre- and postoperatively (Table 2) were somewhat lower than those recommended by others;[5] however, there were only two instances where postoperative wound oozing was caused by insufficient factor replacement. Both cases were easily remedied by slight increases in the dose of factor concentrate.

The type of factor concentrate used to correct factor VIII deficiency is important, as illustrated by our patient who, following transfusion with cryoprecipitate, bled in spite of postoperative levels of factor VIII 30 to 50% of normal. When his therapy was changed to an equivalent amount of commercial factor VIII concentrate the bleeding ceased. Hathaway et al[6] have shown that cryoprecipitate has a large amount of fibrinogen, and that if a hemophiliac is transfused with enough cryoprecipitate, serum fibrinogen levels may also rise, increasing the risk of bleeding even in the presence of normal amounts of factor VIII. In contrast, hyperfibrinogenemia is not observed when commercial factor concentrates are used.

Though we used less factor replacement postoperatively than recommended by others,[5] our results were satisfactory. Emphasis on the necessity for meticulous surgical hemostasis and our economy in use of factor concentrates with less buildup of transfused fibrinogen, which can be detrimental to proper clot formation, were important aspects of our regimen.

Analysis of the corrected factor levels prior to surgery (Table 2) in our patients indicates that hemophiliacs can safely tolerate operative procedures with much lower levels of factor VIII than previously recommended.[5] The factor level can gradually be allowed to drop further during the postoperative period without significantly affecting hemostasis, thereby promoting greater economy in the use of factor concentrates and less rise in serum fibrinogen levels.

Our experience suggests that in a properly prepared hemophiliac patient, carefully executed laryngoscopy and endotracheal intubation can be performed without undue sequelae. Likewise, despite the fact that in a number of our patients an intramuscular preoperative medication was administered as much as 2 hours before the factor correction, no muscle hematomas resulted. This suggests that intramuscular injections may safely be given before factor correction, if the deficient factor is brought up to at least 35% of normal within 2 hours of the injection.

Although none of our patients received methoxyflurane, alleged interactions between methoxyflurane and the clotting process[7] prompted us to examine our records for any possible effect that specific anesthetic agents, notably halothane or enflurane, may have had on intraoperative or postoperative hemostasis. No deleterious effect was correlated with the use of either of these anesthetics. Nevertheless, the anesthetist and surgeon caring for the patient with hemophilia need to be alert to the effect of certain other drugs on the clotting process, as demonstrated by the patient whose wound continued to ooze until indomethacin was discontinued. The most important, as well as the most prevalent, drug which may affect clotting is aspirin, but other drugs such as indomethacin, phenylbutazone, clofibrate, and sulfasoxazole have also been implicated.[8]

The uncomplicated administration of two axillary blocks in our series does not prove the safety of regional anesthesia in hemophiliac patients, but does suggest the need for further assessment of what has previously been regarded as an absolute contraindication.

We conclude that surgery can now be routinely performed on the well-prepared patient with hemophilia A or B, and that the general anesthetics commonly used today have no detectable effect on hemostasis. Corrected levels of deficient clotting factors need not be so high as previously recommended for general or orthopedic surgery, and these levels can safely be allowed to decrease even further postoperatively. Furthermore, the choice of factor VIII concentrate is important, and the interaction of certain drugs with the clotting process needs to be kept in mind.

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ANESTH ANALG
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Bactericidal Effects of Anesthetics

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Inadvertent bacterial contamination of an anesthetic vaporizer poses a potential hazard if such bacteria are subsequently aerosolized and delivered to an anesthetic circuit. This remote hazard would be removed if the volatile anesthetic were itself bactericidal, or if any of the gases flowing through the vaporizer (e.g. nitrous oxide) were bactericidal. Accordingly, we have determined the survival characteristics both of several respiratory pathogens in enflurane and of the sturdiest of those pathogens in other anesthetics. The bacteria were selected for their relative frequency in postoperative patients.

Methods

First Experiment

Six species of bacteria known to be common respiratory pathogens were obtained from the University of California, Berkeley, School of Public Health laboratories: *Corynebacterium diphtheriae, Pseudomonas aeruginosa, Staphylococcus aureus, Proteus vulgaris, Escherichia coli,* and *Serratia marcescens.* No information on strain types was provided. Broth cultures of *C. diphtheriae* and *S. aureus* were raised in nutrient broth (BBL no. 20972), while the other organisms were raised in GN broth (BBL no. 21320). The 24-hour cultures were diluted serially, 10-fold twice into the same broth used for growth, yielding suspensions of ¹⁄₁₀ and ¹⁄₁₀₀ of the concentration of cells provided by the original culture. All procedures were carried out aseptically. One-milliliter samples of the parent culture and of each dilution were inoculated into sterile Vacutainer tubes (BD no. 4700) containing either 1 ml of growth broth or 1 ml of enflurane, yielding a further 2-fold dilution. Residual vacuum was released from the tubes at inoculation, over flame. The tubes were then incubated at 37 C and shaken continuously. Ten minutes, 50 minutes, and 250 minutes after inoculation, a well-mixed 0.1-ml sample was withdrawn by sterile 1-ml syringe and 25-gauge by ⅝″ needle (Sherwood Monoject no. 501-TBLG) and spread on a sterile plate to yield viability counts of the suspensions. The *S. aureus* was plated on mannitol salt agar (BBL no. 21173) and the other bacteria on Trypticase soy agar (BBL no. 21185). The plates were incubated for 48 hours prior to counting colonies.

Second Experiment

The effects of halothane, enflurane, methoxyflurane, isoflurane, chloroform, ether, and nitrous oxide on survival of *S. aureus* strain 81 were tested. *S. aureus* was obtained from the University of California, Berkeley, School of Public Health laboratories. Serial dilutions of a standard broth culture were prepared as before except that 3- to 4-fold rather than 10-fold dilutions were used. One milliliter of each of the three concentrations of bacteria was aseptically inoculated into tubes containing 1 ml of each of the six liquid anesthetics, yielding a further 2-fold dilution. Residual vacuum was released as previously described. The nitrous oxide tubes were prepared as follows: two sterile 16-gauge by 1½″ needles capped with sterile 3-way stopcocks were inserted through the rubber stopper. Then 76.2% nitrous oxide, balance oxygen was delivered to the tube via one of the stopcocks, the remaining needle and stopcock acting as a vent. Nitrous oxide was flushed through the tube for 2 minutes at which time both stopcocks were simultaneously closed. The needles and stopcocks were left in position for the duration of the experiment. One milliliter of bacterial suspension was injected into the nitrous oxide-oxygen tubes. Samples from all tubes were drawn and plated as previously described, except that we drew samples at 12.5, 50, and 100 minutes.

Results

In the first experiment, no organism survived 250 minutes of exposure to enflurane (Table 1). The annotation "TMTC," for "too many to count," indicates that the colonies on these plates had a high incidence of confluent growth (colonies spreading into each

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TABLE 1
Bactericidal Effect of Enflurane*

Time	Dilution	*Staphylococcus aureus*		*Corynebacterium diphtheria*		*Escherichia coli*		*Serratia marcescens*		*Proteus vulgaris*		*Pseudomonas aeruginosa*	
		Broth	Enflurane	Broth	Enflurane	Broth	Enflurane	Broth	Enflurane	Broth	Enflurane	Broth	Enflurane
min													
10	10^0	TMTC	TMTC	52	13	TMTC	TMTC	TMTC	TMTC	TMTC	TMTC	TMTC	0
10	10^1	TMTC	TMTC	5	0	TMTC	310	TMTC	—†	TMTC	330	TMTC	0
10	10^2	TMTC	TMTC	1	0	TMTC	13	TMTC	180	TMTC	31	TMTC	0
50	10^0	TMTC	TMTC	14	0	TMTC	0	TMTC	0	TMTC	0	TMTC	0
50	10^1	TMTC	325	0	0	TMTC	0	TMTC	0	TMTC	0	TMTC	0
50	10^2	TMTC	34	0	0	TMTC	0	TMTC	0	TMTC	0	TMTC	0
250	10^0	TMTC	0	0	0	TMTC	0	TMTC	0	TMTC	0	TMTC	0
250	10^1	TMTC	0	0	0	TMTC	0	TMTC	0	TMTC	0	TMTC	0
250	10^2	TMTC	0	0	0	TMTC	0	TMTC	0	TMTC	0	TMTC	0

* Liquid enflurane proved lethal to all bacteria at all inoculum dilutions. Time is minutes of exposure to the liquid anesthetic. Either there was no dilution of inoculum (10^0), a 10-fold dilution (10^1), or a 100-fold dilution (10^2) prior to mixing with an equal volume of inoculum. Values under "broth" (equals control) or enflurane indicate the surviving bacteria per 0.1 ml of suspension. TMTC indicates that there were too many bacteria to count (in excess of 500 colonies per plate)

† Sample was lost.

TABLE 2
Bactericidal Effect of Chloroform, Enflurane, Ether, Halothane, Isoflurane, Methoxyflurane, and Nitrous oxide*

Time after inoculation	*S. aureus* concentration	Control	Methoxyflurane	Isoflurane	Enflurane	Nitrous oxide
min						
12.5	High	191	74	3	141	224
12.5	Medium	51	18	0	41	57
12.5	Low	20	8	0	3	16
25	High	164	32	1	80	272
25	Medium	65	21	0	50	72
25	Low	15	0	0	5	20
50	High	183	19	0	74	342
50	Medium	60	7	0	30	93
50	Low	16	1	0	3	34
100	High	323	0	0	17	415
100	Medium	109	1	0	9	141
100	Low	32	0	0	3	43

* Values in the columns under the various treatments (including control) indicate the plate counts of *S. aureus* after 12.5, 25, 50, and 100 minutes of treatment. For each determination 0.05 ml of inoculum was spread on the plate. "High" *S. aureus* concentration equals about 200 bacteria per 0.05 ml; "Medium" equals about 60 bacteria per 0.05 ml; and "Low" equals about 20 bacteria per 0.05 ml. No colonies were obtained at any of the above times from suspensions exposed to liquid chloroform, ether, or halothane.

other), making an accurate count impossible. The controls were acceptable, except for *C. diphtheriae.* Other than *C. diphtheriae's* known relative fragility,[1] no explanation of the *C. diphtheriae* control results can be offered. With this exception, there was no evidence of attrition in the control cultures at any dilution. The effect of dilution was present but not quantifiable in control cultures, due to the high concentrations of bacteria present. The effect of dilution was quantifiable in the anesthetic-treated cultures.

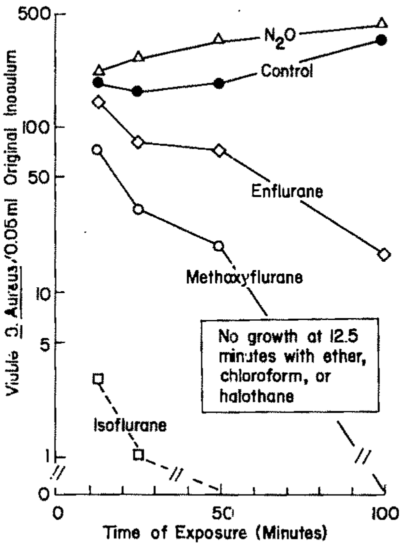

FIG 1. Survival of *S. aureus* (strain 81) bacteria decreased with duration of exposure to all liquid anesthetics. The bactericidal effect varied between anesthetics: enflurane and methoxyflurane were least effective whereas isoflurane, chloroform, ether, and halothane rapidly produced death. Survival of bacteria exposed to nitrous oxide paralleled survival of control bacteria. The original inoculum contained about 200 bacteria per 0.05 ml (high level inoculum).

In the second experiment a bactericidal effect was

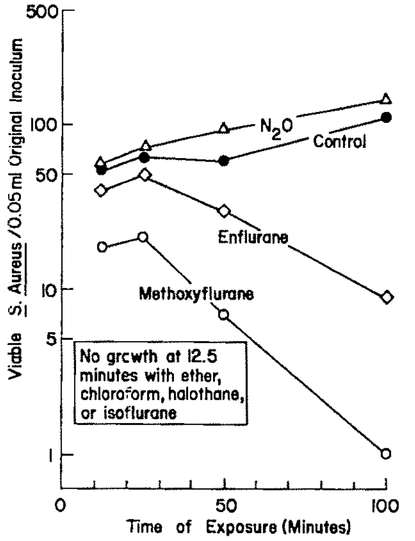

FIG 2. Reduction of the original inoculum to about 50 bacteria per 0.05 ml (medium level) did not change the relative lethality of the anesthetics tested.

observed with all anesthetics except nitrous oxide (Table 2, Figs 1 and 2). These figures correspond to the high and medium level inocula reported in Table 2. The low level inoculum is not illustrated due to the small counts obtained. The anesthetics differed in their potency with chloroform, ether, and halothane killing *S. aureus* in the shortest period of time, isoflurane next most rapid, methoxyflurane next, and enflurane least.

Discussion

Our study examined whether inadvertent bacterial contamination of an anesthetic vaporizer could subsequently be transmitted to a patient. Our data suggest that this is unlikely. Exposure to liquid enflurane was bactericidal to all organisms tested, even with the continued presence of nutrient broth. *S. aureus* was the hardiest of the bacteria studied and was therefore chosen for the subsequent experiments. The second experiment revealed that other liquid anesthetics were yet more potent bactericides than enflurane. This suggests that bacteria contaminating a vaporizer or opened container would be destroyed and thus would not constitute a potential source of patient infection. During filling, organisms might be flushed into the vaporizer from the funnel which directs anesthetic into the vaporizer. Contamination of the funnel may result from direct contact (e.g. by touch) or from an airborne source (e.g. dust particles or aerosols).

TABLE 3

Anesthetic Vapor Pressure (P_{vap})/MAC Ratio vs Survival*

Anesthetic	P_{vap}/MAC	Survival
		min
Halothane	72.6	<12.5
Chloroform	56.4	<12.5
Isoflurane	43.8	12.5
Ether	35.5	<12.5
Methoxyflurane	32.0	100
Enflurane	20.6	>100

* Ratio of anesthetic vapor pressure (P_{vap}) as a percent of one atmosphere to MAC is roughly related to the duration of survival of *S. aureus* when exposed to saturated solutions of anesthetic. Duration of survival was taken to be the time of exposure to anesthetic required to reduce the viable bacterial count to 1 or 0.

The reason for the differences in the bactericidal effects of the anesthetics is unclear. It does not relate to either lipid or aqueous solubility of the agents.[2] There is a rough correlation between the vapor pressure/MAC ratio[3] and lethality (Table 3). These data suggest a "lethality" threshold of about 20 to 35 for P_{vap}/MAC. Below this threshold bacteria may survive for fairly long periods. Other respiratory pathogens might warrant examination. These include *Mycobacterium tuberculosis* and members of the Bacillus genus. The possibility of viral survival was not investigated. None of the anesthetics tested is sterilized prior to packaging, nor was any sterilization attempted prior to use in the experimental procedures. No contaminating colonies were seen on any of the plates. Aside from reassuring the authors as to their aseptic technique, this demonstrates that no contamination arose from the anesthetics themselves.

ACKNOWLEDGMENTS

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Antagonism of Neuromuscular Blockage by Theophylline

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Theophylline has recently been reported to antagonize nondepolarizing neuromuscular block in animals.[1] To our knowledge, however, there has been no report of theophylline affecting neuromuscular transmission in humans. In this report we describe difficulty in achieving a nondepolarizing neuromuscular block in a patient who was receiving aminophylline by constant infusion.

Report of a Case

A 21-year-old comatose woman, weighing 45 kg, suffered smoke inhalation and hypoxic brain injury 4 days prior to admission to the intensive care unit. An endotracheal tube was in place and she was breathing spontaneously through a T-piece. A chest x-ray showed diffuse patchy infiltrates bilaterally. The electrocardiogram and serum sodium, potassium, chloride, calcium, and magnesium levels were within normal limits. The respiratory rate was 55 breaths per minute. The minute ventilation was 16.4 L. Arterial blood gases at F_IO_2 0.4 were P_{O_2}, 167 torr; P_{CO_2}, 63 torr; pH 7.27. An infusion of aminophylline at a rate of 1.55 mg/kg/hr (69.9 mg/hr) was being administered because of severe bronchospasm and this dose had been unchanged for the previous 48 hours. A blood theophylline level at this infusion rate was 35 mg/L (therapeutic range 10–20 ml/L). Other medications included hydrocortisone 100 mg every 6 hours IV and cimetidine 300 mg every 6 hours IV.

Because of the patient's respiratory status, it was decided that controlled mechanical ventilation was necessary and muscular paralysis with pancuronium was planned. Six milligrams of pancuronium were given via a 16-g central intravenous line but after approximately 5 minutes the patient continued to hyperventilate and muscular paralysis did not occur. A peripheral nerve stimulator placed over the patient's left ulnar nerve showed sustained tetanus at a frequency of 50 Hz and sustained twitch height at a frequency of 0.5 Hz (train of 4). Two fresh ampules of pancuronium were obtained from a refrigerated supply and an additional 16 mg of pancuronium were given over the next 20 minutes without change in respiratory status or response to nerve stimulation. The patient was then given succinylcholine, 100 mg IV; fasciculations were not observed and within 1 minute spontaneous ventilation ceased. Subsequent to the succinylcholine, no response to tetanic or twitch stimuli were observed for approximately 10 minutes. Spontaneous ventilation then returned and response to the nerve stimulator was similar to the presuccinylcholine period. The patient was then given d-tubocurarine in 3-mg increments to a total dose of 18 mg at which time muscular paralysis was clinically evident. At this time nonsustained tetanus, posttetanic facilitation, and evidence of twitch depression was seen upon nerve stimulation. She was then ventilated without difficulty by a Bennett MA-1 respirator. The patient subsequently required only 3 mg of pancuronium to be mechanically ventilated over the next 10 hours; however, during this time the aminophylline infusion had been decreased to 0.89 mg/kg/hr (40 mg/hr). Unfortunately, a theophylline blood level was not obtained at this infusion rate

Discussion

This patient demonstrated marked resistance to the neuromuscular blocking effects of pancuronium. Potential causes of failure of drug action that were excluded were: (1) failure of the drug to enter the bloodstream—this is unlikely as pancuronium was injected through a functioning central venous route, and (2) loss of potency of drug—this is unlikely as 16 mg of pancuronium were obtained from a refrigerated supply that was used without problems with other patients. Since the patient was receiving a large amount of theophylline, antagonism of pancuronium by this phosphodiesterase inhibiter may explain the unusual hyposensitivity to pancuronium.

Using a cat soleus muscle preparation, Dretchen et al[1] demonstrated an increase in the force of contraction after intraarterial injection of theophylline in doses ranging from 100–600 μg/kg. They also showed reversal of a d-tubocurarine neuromuscular block at theophylline doses greater than 200 μg/kg with complete reversal at 400 μg/kg. Several recent studies[2–4] have examined the relation between theophylline, the cyclic nucleotide system, and the neuromuscular junction. Standaert and Dretchen[5] have proposed that the nerve action potential is responsible for stimulating activity of adenyl cyclase, the enzyme responsible for cyclic AMP (cAMP) production. They hypothesize that the increased cAMP at the prejunctional level promotes a series of intermediary steps which leads to neurotransmitter release.[5] Theophylline competitively inhibits phosphodiesterase which is responsible for the degradation of cAMP to 5′-AMP. Therefore, cAMP levels would increase, resulting in increased

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transmitter release and muscle contraction. A nondepolarizing neuromuscular blocking drug that acts by competitive inhibition with acetylcholine would then be antagonized. On the other hand, block by depolarizing relaxants (e.g. succinylcholine) would be potentiated by phosphodiesterase inhibitors.

In our patient, aminophylline was infused at a rate of 1.55 mg/kg/hr and the plasma theophylline level was 35 mg/L. This plasma level is consistent with the infusion rate. Piafsky and Ogilvie[6] demonstrated that intravenous infusions of aminophylline at 0.90 and 1.35 mg/kg/hr result in plasma theophylline levels ranging from 5–15 and 10–20 mg/L, respectively.

Theophylline plasma levels were not measured in Dretchen's animal study and therefore comparisons with our patient's level are not possible. If Dretchen's study could be extrapolated to humans, this would provide a plausible explanation of failure to establish a nondepolarizing neuromuscular block with pancuronium in this patient. When the aminophylline infusion rate was decreased neuromuscular block was established easily, further supporting this proposed explanation. Ideally, blood levels of pancuronium and theophylline along with appropriate dose response curves would have been required to verify these conclusions.

Although intravenous hydrocortisone has been reported to partially antagonize the neuromuscular blockade from pancuronium, in a patient with adrenocortical insufficiency,[7] this is unlikely to have been a factor in this case. In the patient presented here there was no evidence of adrenocortical insufficiency and steroid administration was continued after theophylline was stopped without further difficulty in achieving neuromuscular blockade.

In summary, a case has been reported where a constant aminophylline infusion has been implicated as the cause of failure to produce a nondepolarizing neuromuscular block despite large doses of pancuronium. This antagonism appeared to have occurred with theophylline levels in excess of the recommended therapeutic range. The effect of lower theophylline blood levels on neuromuscular transmission in humans remains to be investigated.

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Stopcock Contamination

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The source of septicemia as nosocomial infection is often difficult to define[1-4] and is frequently associated with high mortality.[5] Stopcocks are commonly used in the practice of anesthesia to assist in pressure monitoring and for the administration of drugs, fluids, and transfusions. We examined their potential as a source for systemic contamination.

Methods

First Study Cultures

The first study included 103 stopcocks that had been used by the anesthesiologist during the operative period and were removed upon the patient's arrival in the recovery room. The fluid stream channels were cultured by flushing with 10 ml of tryptic soy nutrient broth and aerobically incubating for 48 hours. Visual clouding of the broth was interpreted as positive contamination. Fourteen unused stopcocks (controls) were cultured in the same manner.

Second Study Cultures

A second study of 49 used and 4 unused control stopcocks were collected and cultured in a similar manner, but the broth was added to 15 ml of melted tryptic soy agar mixed and poured into a sterile Petri dish which was incubated aerobically at 35 C for 48 hours. The plates were examined macroscopically and colonies checked under a 30X disecting stereomicroscope. The number of colonies and the types of organisms were documented.

Results

All unused control stopcocks were negative for growth. Fifty positive cultures resulted from the first 103 stopcocks that were cultured in broth only (48.5%). The degree of cloudiness could not be interpreted as a method for determining the degree of contamination.

Not all positive cultures were studied for organism type. However, of those identified there was a preponderance of *Staphylococcus epidermidis* coagulase negative. Other types of organisms included aerobic bacilli, enterococcus, and diphtheroids.

Twenty positive cultures were obtained from the 49 stopcocks cultured with agar plates (40%). On the 20 plates the numbers of organisms were: one had four colonies; one had five colonies; one had six colonies; one had seven colonies; one had 13 colonies; one had 14 colonies; one had 16 colonies; one had 27 colonies; two had two colonies; two had three colonies; and eight had one single colony. The types of organisms included: Micrococcus on two plates; *S. epidermidis* on 19 plates; Gram-negative bacillus (nonfermenting) on one plate; *Staphylococcus aureus* on two plates; and *Escherichia coli* on one plate.

Eighty-five of the stopcocks in the study were not packaged with limb covers; 42 (40%) of these were positive. Sixty-seven stopcocks were originally packaged with covers; 28 (41.8%) were positive. Thirty-five (52%) of the 67 stopcocks originally supplied with limb covers had the original cover or a syringe on the side limb when cultures were made; of this group 16 (45%) were positive. Thirty-two (48%) of the 67 had the side limb uncovered at the time of culture; of these 12 (37.5%) were positive.

Discussion

These studies were carried out over a 3-year period. During this interval personnel were aware of concern about stopcock contamination and were asked to practice special care in their use. In spite of this knowledge numerous breaks in sterile technique were observed, as for example, allowing an uncovered limb of the stopcock to fall and touch a nonsterile area, or allowing the finger tips to contact an area of the stopcock that would later be contacted by a syringe or intravenous line. The small size and the short limbs on stopcocks make them tedious to handle properly; however, stopcocks used by a few individual anesthesiologists in the study had consistantly negative cultures. Prevention of contamination could be achieved under clinical conditions.

The providing of cover caps with the stopcocks did not decrease the incidence of contamination. The

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covers were often dropped or discarded; in some cases a syringe was used to act as a cover substitute. There was an overall contamination rate of 46% in the combined studies, compared to 41.8% of stopcocks initially provided with covers. The high incidence of organisms common to the skin suggests that the fingers of the anesthetist are a common source of contamination. There was no readily defined relationship between the incidence of contamination and duration of use in the operating room.

Our method of culture did not ensure or validate that all organisms in the stopcock were removed. We are also aware that the number of colony-forming units does not necessarily reflect the number of organisms present. One colony may form from one or a few individual bacterial cells. No attempt was made to determine whether contamination extended downstream from the stopcock.

During the study periods one patient developed *S. epidermidis* septicemia postoperatively, but direct relationship to the use of the stopcock could not be established because the culture was discarded before there was awareness of the patient's problem. There were no other cases of septicemia among the study group. There was not adequate patient follow-up to evaluate a possible relationship between phlebitis and contaminated stopcocks.

In summary, we found that routine use of stopcocks during anesthesia for the administration of fluids and drugs was associated with a contamination rate of 46%.

ACKNOWLEDGMENT

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Erratum

In the paper "Pharmacokinetics of Drugs Administered Intravenously" by Carl C. Hug, Jr. (*Anesthesia and Analgesia* 57: 704–723, 1978) there is an error on p 722, Fig 10.

The scale of the ordinate (vertical axis) is incorrect. Instead of a logarithmic scale as shown, it should be arithmatic; that is, the numbers should read from the bottom up 0, 1, 2, 3, 4, 5, 6. C_1^{ss} will equal 3 at an infusion rate of Q and will equal 6 at an infusion rate of 2Q.

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Relief of Pulmonary Congestion by Sublingual Nitroglycerin in Patients with Mitral Valve Disease

Ercument A. Kopman, MD*

Acute pulmonary congestion may occur in patients with valvular heart disease despite vigorous medical therapy (digitalis-diuretic). Further increases in digitalis or diuretic dosage are then ineffective and may lead to problems of toxicity.[1] Sublingual nitroglycerin (SNG) has been shown to be beneficial in emergency treatment of pulmonary edema due to myocardial infarction and valvular heart disease.[2-4] In two patients with acute pulmonary congestion due to valvular heart disease (ruptured chorda tendenea and mitral stenosis) undergoing valve replacement, we used SNG to relieve pulmonary edema. In both patients, within 4 to 5 minutes after administration of SNG (0.3 mg), systolic pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP) decreased significantly with concomitant improvement of clinical symptoms.

Report of Two Cases

Case 1

A 71-year-old woman weighing 47 kg was hospitalized because of heart murmur, shortness of breath, and palpitations. A left ventriculogram revealed significant prolapse of the posterior and anterior leaflets of the mitral valve and wide open mitral valve regurgitation. There was moderate elevation of left ventricular end diastolic pressure (LVEDP) (15 torr) with a large V wave (47 torr), which is consistent with significant mitral regurgitation. Mean left atrial pressure was 23 torr and ejection fraction was 61%. Right heart catheterization revealed normal right atrial pressures and moderate elevation of right ventricular (43/6 torr) and pulmonary artery pressures (39/17 torr). She was scheduled for a mitral valve replacement. The night before surgery, however, despite optimal medical treatment, she had an episode of pulmonary edema.

Premedication consisted of 10 mg of morphine and 0.4 mg of scopolamine, intramuscularly 1 hour before induction of anesthesia. On arrival in the induction room, the patient was in acute distress associated with shortness of breath and orthopnea. A #20 Medicut plastic cannula was placed into the right radial artery for monitoring of arterial pressure and blood gas sampling. A #7 French Swan-Ganz catheter was inserted percutaneously under local anesthesia into the pulmonary artery via the right internal jugular vein for hemodynamic measurements. The arterial pressure was 160/80 torr, heart rate was 90/min, the central venous pressure 10 torr, right ventricle and pulmonary artery systolic pressure 60 torr, and PCWP 35 torr. To avoid further aggravation of her condition before cardiopulmonary bypass began, nitroglycerin (0.8 mg) dissolved with 1 ml of saline was administered sublingually. Within 5 minutes systolic pressure decreased from 160 to 110 torr, PAP from 60 to 32 torr, and PCWP from 35 to 15 torr. Cardiac index increased slightly from 2.62 to 2.87 $L/min/m^2$. Anesthesia was then induced with 10 mg of diazepam and 100 mg of thiopental and maintained with 1.5 mg/kg of morphine and N_2O:O_2 (50:50). Arterial pressure, central venous pressure, PAP, and PCWP all remained stable until cardiopulmonary bypass was started (approximately 30 minutes).

Case 2

A 40-year-old white woman weighing 68 kg was hospitalized for cardiac catheterization to evaluate her mitral stenosis. Cardiac catheterization revealed a tight mitral stenosis, minimal aortic regurgitation, and normal coronary arterial system. The PAP was 63 torr; PCWP was 25 torr. Because of the symptoms associated with severely tight mitral stenosis, the patient was scheduled for mitral valve surgery. She was on a maintenance dose of digitalis because of atrial fibrillation. Premedication consisted of 10 mg of morphine sulfate and 0.4 mg of scopolamine intramuscularly 1 hour prior to surgery.

On arrival in the induction room, the patient was in acute distress associated with shortness of breath, breathing oxygen through a mask. An arterial cannula and a Swan-Ganz thermodilution catheter were inserted with the same technique as previously described. Arterial pressure was 110/80 torr and heart rate 89/min. PAP was 65 torr; PCWP was 28 torr. Nitroglycerin (0.8 mg) was administered sublingually. Within 4 minutes PAP decreased from 65 to 35 torr; PCWP decreased from 28 to 16 torr. Arterial pressure and heart rate did not change. Cardiac output was not measured. No significant hemodynamic changes occurred before cardiopulmonary bypass (approximately 35 minutes).

Discussion

The main objective in treating pulmonary congestion in patients with heart valve disease is to provide immediate relief by reducing left ventricular end-diastolic pressure-left atrial pressure and, consequently, pulmonary capillary pressure. This can be achieved either by increasing contractility (digitalis) or in some cases by reducing afterload and/or preload (vasodilators). In patients with valvular heart disease (except patients with mitral stenosis without left heart failure), pulmonary congestion is almost always the result of elevated LVEDP. Since most patients have been on digitalis and the optimum contractile state has already been achieved, further increase in dosage would not

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be effective in relieving pulmonary congestion. In mitral regurgitation, the magnitude of the regurgitant flow is determined by a pressure gradient between left ventricle and the left atrium. The pressure gradient between the left ventricle and the left atrium during systole is much higher than that between the left ventricle and the aorta. There is a large reflux into the left atrium during ventricular systole. Therefore, reduction of aortic impedence to left ventricular ejection will tend to decrease the regurgitant flow to the left atrium and increase forward flow with a concomitant reduction in PCWP and PAP.[5, 6]

On the other hand, mitral stenosis is unique in that pulmonary edema often occurs relatively early in the life history of the disease, when the right ventricle has good function, the left ventricle is small and LVEDP is not high. Maintenance of blood through the narrowed mitral orifice is determined by the excess of left atrial over left ventricular pressure in diastole. The greater the flow, the higher left atrial and pulmonary capillary pressure for a given degree of mitral stenosis. The rise in pulmonary capillary pressure is due to a restricted flow into the left ventricle rather than left heart failure. In this group of patients, a decrease in venous return would reduce the pressure in both the overdistended left atrium and pulmonary capillaries.

In the first patient with mitral regurgitation, the mechanism for the nitroglycerin-mediated improvement in pulmonary congestion was probably related primarily to the peripheral venous[7-9] and arterial dilation[10, 11] produced by the drug. The dramatic fall in PAP and PCWP probably was due to a decrease in regurgitant flow,[5, 6] increase in cardiac output,[5, 6, 12] decrease in pulmonary vascular resistance,[8, 13, 14] decrease impedance to ejection,[4, 5, 11, 12] decrease in venous return,[7-9] and a decrease in LVEDP.[14]

In the patient with mitral stenosis, improvement in pulmonary congestion was probably due to reduction in left atrial pressure, pulmonary arterial pressure, and pulmonary capillary pressure produced either by venous pooling[7-9] or relaxation of the pulmonary venomotor tone.[8, 13, 14] The duration of action of sublingual nitroglycerin may vary between 30 minutes to 1 hour.[15, 16] This time interval between drug administration and cardiopulmonary bypass is long enough to provide a considerable hemodynamic stability before extracorporeal circulation begins.

In both patients nitroglycerin produced an immediate clinical and hemodynamic improvement despite the differences between the mechanisms responsible for the development of pulmonary congestion. This report suggests that administration of sublingual nitroglycerin is a simple and effective technique in the emergency treatment of pulmonary congestion in patients with mitral valve diseases.

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Defect in Oxygenation Associated with Mannitol

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Mannitol is an osmotic diuretic used during intracranial surgical procedures to reduce brain size and thereby to improve operating conditions. It is distributed in the extracellular fluid and therefore can be accompanied by an acute expansion of extracellular fluid volume.[1] This may have a detrimental effect on arterial oxygenation as illustrated by the following patients.

Case Reports

Case 1

A 59-year-old man weighing 80 kg was scheduled for a left craniotomy because of right-sided weakness. The remainder of his physical examination was normal. A complete blood count (CBC), chest x-ray, electrocardiogram (ECG), and blood chemistries were also normal.

On the morning of surgery, he was premedicated with meperidine, 50 mg, and atropine, 0.6 mg im. In the operating room, he was preoxygenated, and anesthesia was induced with thiopental, 300 mg. Succinylcholine, 100 mg, was used to facilitate intubation of his trachea. Anesthesia was maintained with enflurane and nitrous oxide-oxygen (3:2 L/min) to provide a calculated FI_{O_2} of 0.4. Lactated Ringer's solution was infused at a rate of 2.0 ml/kg/hr. Thirty minutes after induction of anesthesia and positioning of the patient, arterial blood gases were P_{O_2} 141 torr, P_{CO_2} 30 torr, and pH 7.54. The calculated alveolar-arterial oxygen gradient ($A\text{-}aD_{O_2}$) was 101 torr. It was calculated by the alveolar gas equation: $PA_{O_2} = (P_B - P_{H_2O})FI_{O_2} - Pa_{CO_2}$. Next 20% mannitol (500 ml) was rapidly infused. Thirty minutes after the mannitol infusion arterial blood gas analysis revealed P_{O_2} 90 torr, P_{CO_2} 35 torr, and pH 7.45; the calculated $A\text{-}aD_{O_2}$ was 147 torr. During this time neither ventilation nor patient position were changed. One hour after the mannitol infusion arterial blood gases were P_{O_2} 165 torr, P_{CO_2} 35 torr, pH 7.45, and the calculated $A\text{-}aD_{O_2}$ was 72 torr. A left-sided tumor was removed during a 3-hour operation, at the conclusion of which the patient was taken to the recovery room in satisfactory condition.

Case 2

A 66-year-old man weighing 67 kg was admitted with headaches and neck stiffness. Arteriograms revealed an arteriovenous malformation. Physical examination revealed mild pulmonary emphysema but was otherwise normal. CBC, ECG, and blood chemistries were normal. A chest x-ray showed mild chronic obstructive pulmonary disease.

In the operating room anesthesia was induced with thiopental, 175 mg. Succinylcholine, 80 mg, was used for endotracheal intubation. Anesthesia was maintained with enflurane and nitrous oxide-oxygen (3:2) with an FI_{O_2} of 0.4. Thirty minutes after induction and positioning of the patient, arterial blood gases were P_{O_2} 148 torr, P_{CO_2} 38 torr, and pH 7.48 with a calculated $A\text{-}aD_{O_2}$ of 76 torr. Then 20% mannitol, 500 ml, was infused. Position and ventilation remained constant during the infusion period. Thirty minutes following the mannitol infusion arterial blood gases were P_{O_2} 93 torr, P_{CO_2} 32 torr, pH 7.50, and the calculated $A\text{-}aD_{O_2}$ 147 torr. One hour after the completion of the mannitol infusion arterial blood gases were P_{O_2} 142 torr, P_{CO_2} 33, pH 7.49, and the calculated $A\text{-}aD_{O_2}$ 97 torr. Lactated Ringer's solution was administered at a rate of 2.0 ml/kg/hr. Anesthesia was satisfactory and the patient was taken to the recovery room 6 hours later.

Case 3

A 65-year-old man weighing 80 kg was scheduled for a right craniotomy after being admitted to the hospital with left-sided paralysis. On physical examination he had distant breath sounds upon auscultation; the remainder of the physical examination was normal. CBC, ECG, chest x-ray, and blood chemistries were normal.

After preoperative medication with diazepam, 10 mg, anesthesia was induced with thiopental, 350 mg. The trachea was intubated after succinylcholine, 100 mg. Anesthesia was maintained with halothane, and nitrous oxide-oxygen (3:2) to provide an FI_{O_2} 0.4. Thirty minutes after induction arterial blood gases were P_{O_2} 138 torr, P_{CO_2} 27 torr, pH 7.48, and the calculated $A\text{-}aD_{O_2}$ 109 torr. Then 20% mannitol, 500 ml, was rapidly infused and 30 minutes later arterial blood gases were P_{O_2} 76 torr, P_{CO_2} 26 torr, pH 7.51, and the calculated $A\text{-}aD_{O_2}$ 172 torr. One hour after completion of the mannitol infusion arterial blood gases were P_{O_2} 125 torr, P_{CO_2} 29 torr, and pH 7.49; the calculated $A\text{-}aD_{O_2}$ was 118 torr. Ventilation and position remained unchanged during this period. Lactated Ringer's solution was infused at a rate of 3.5 ml/kg/hr. After 3 hours a frontoparietal tumor was removed and the patient had a satisfactory recovery.

Discussion

In each of the above cases, a substantial if ephemeral decrease in the arterial oxygen tension was observed immediately after infusion of a large amount of mannitol at a time when FI_{O_2}, position, and other factors known to affect Pa_{O_2} were kept constant. As a result, the calculated alveolar-arterial oxygen gradient ($A\text{-}aD_{O_2}$) increased markedly.

Intracranial lesions can cause pulmonary edema and thus decrease Pa_{O_2}. Survival following this type of pulmonary edema is rare; however, this reflects the

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severe nature of the insult that precipitates this complication. The pathogenesis of neurogenic pulmonary edema remains obscure, but may involve the hypothalamus, medulla, vagus, and sympathetic nerves innervating postcapillary pulmonary venules.[2] The defect in oxygenation in our patients was transitory with oxygen tensions and A-aD_{O_2} values that returned to original pre-mannitol values within 1 hour. This appears to preclude a neurogenic basis of the observed decrease in Pa_{O_2} in these three patients.

Mannitol is pharmacologically inert by conventional criteria and has been advocated in the therapy of respiratory distress syndrome to improve gas exchange.[3] Williams et al[4] have shown in an isolated lung-perfusion model that perfusion of the lungs with a hyperosmolar electrolyte solution containing 7½% dextrose can reduce pulmonary extravascular water with improvement of the arterial oxygen tension. On the other hand, Reif et al[5] reported an unexpected deleterious effect of mannitol. Using an isogravimetric perfused canine lung preparation, they found that 10% mannitol significantly increased lung weight gain and pulmonary capillary pressure and decreased pulmonary venous oxygen tension and pulmonary compliance. The difference between these findings and those of Williams et al may be related to the fact that 10% mannitol is more hyperosmolar than the 7½% dextrose-electrolyte solution.

These three cases illustrate brief but substantial interference with arterial oxygenation following infusions of large amounts of mannitol. The increase in the A-aD_{O_2} may reflect interstitial edema due to the expansion of the extracellular volume and increased hydrostatic pressure.[6] With the onset of diuresis, the extracellular volume as well as the hydrostatic pressure are reduced and oxygenation is improved while brain size is reduced.

The frequency of the increase in A-aD_{O_2} associated with mannitol cannot be established by these preliminary observations, but the incidence should be determined by further studies. These observations should be a consideration in those patients for whom changes in oxygen tensions are critical.

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Bilateral Pneumothorax from Suction Applied to a Ventilator Exhaust Valve

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Several possible causes of pneumothorax and its sequelae have been well described.[1-3] Its occurrence during anesthesia is potentially catastrophic if not quickly recognized and corrected. This is a report of a case of bilateral tension pneumothorax, pneumomediastinum, and subcutaneous emphysema which rapidly developed following an intraoperative change in the ventilator scavenger system.

Report of a Case

A 41-year-old woman with chronic myelogenous leukemia was scheduled for an elective splenectomy.

Physical examination revealed a healthy appearing woman, weighing 60 kg, without remarkable physical findings. The EKG and chest x-ray were normal. All pertinent laboratory data were within normal limits. The day before surgery, the administration of heparin, 5000 units subcutaneously every 12 hours, was started. Before induction of anesthesia, vital signs included a blood pressure of 110/70 mm Hg and a heart rate of 66/min. Anesthesia was induced using 250 mg of 2.5% thiopental sodium. After 2 minutes of assisted ventilation with 100% O_2, 80 mg of succinylcholine were given and under direct vision, the trachea was easily intubated using an 8-mm orotracheal tube and the cuff was inflated with 5 ml of air. The patient was manually ventilated and the chest was noted to rise symetrically and breath sounds were heard equally well bilaterally.

Anesthesia maintenance was started using an oxygen-nitrous oxide mixture at 5 L/min with an $F_{I_{O_2}}$ of 0.4 and enflurane at a concentration of 2%. Pancuronium, 3 mg, was given for muscle relaxation. A Foregger anesthesia machine (model BC) and an Ohio enflurane vaporizer were used. After 10 minutes of manual ventilation, a Foregger anesthesia ventilator (model 910) was used with a tidal volume of 650 ml, a rate of 10 cycles/min, and end inspiratory pressure of 15 cm. H_2O. With the onset of surgical stimulation the blood pressure stabilized at between 110 to 120/80 mm Hg with a heart rate of 90 to 96/min. An additional 1 mg of pancuronium was given 35 minutes after the initial dose. Approximately 50 minutes after induction of anesthesia it was necessary to correct a disconnection between the anesthesia ventilator and the scavenger system. The technician replaced the loose hose connector on the ventilator exhaust port with a slightly larger one and reconnected the negative pressure scavenger hose without any immediately apparent effects on the system. Within 2 to 3 minutes the patient developed a sudden tachycardia followed by a bradycardia. Numerous ventricular premature beats were noted and there was a simultaneous drop in blood pressure. At approximately the same time the surgical team noted a downward displacement of the liver into the abdomen and the anesthesia ventilator made labored and prolonged inspiratory sounds. The end-expiratory pressure was noted to be 35 cm H_2O. The patient was seen to develop a sudden puffiness of the neck, face, and eyelids. A diagnosis of tension pneumothorax was made immediately by the anesthesiologist. The surgical team responded by incising the left hemidiaphragm. A large amount of trapped gas was released. The patient was disconnected from the ventilator and manually ventilated with 100% O_2. Within 1 minute, the vital signs had returned to normal. Before continuing with the surgery, bilateral chest tubes were inserted as it was not certain whether the pneumothorax was unilateral at that time. Following insertion of the right chest tube, it was apparent that a right pneumothorax had also developed. The surgical procedure was then completed without further incident. At the end of the case, reversal of the muscle relaxant was accomplished using atropine, 1.0 mg, and pyridostigmine, 10 mg. The patient resumed spontaneous respirations. Extubation was carried out in the recovery room within an hour of admission. A chest x-ray taken immediately postoperatively showed a small pneumomediastinum with subcutaneous emphysema but no evidence of pneumothorax. Later chest x-rays were unremarkable. The chest tubes were removed between 48 to 72 hours postoperatively without problems. The subcutaneous emphysema was almost completely resorbed within 2 days. The remainder of the postoperative course was unremarkable.

Discussion

The legitimate concern about operating room pollution with anesthetic gases had led to the development of gas evacuation systems. One of the techniques currently employed is the application through various means of subatmospheric pressure to exhaust ports in anesthesia systems. This has, however, led to the generation of other problems. The design features of some older and contemporary equipment have not been sufficiently flexible to accomodate new requirements. In a recent publication, Sharrock and Leith[4] presented data which indicated the existence of potential hazards if anesthesia circle scavenger valves of various designs were connected to negative pressure.

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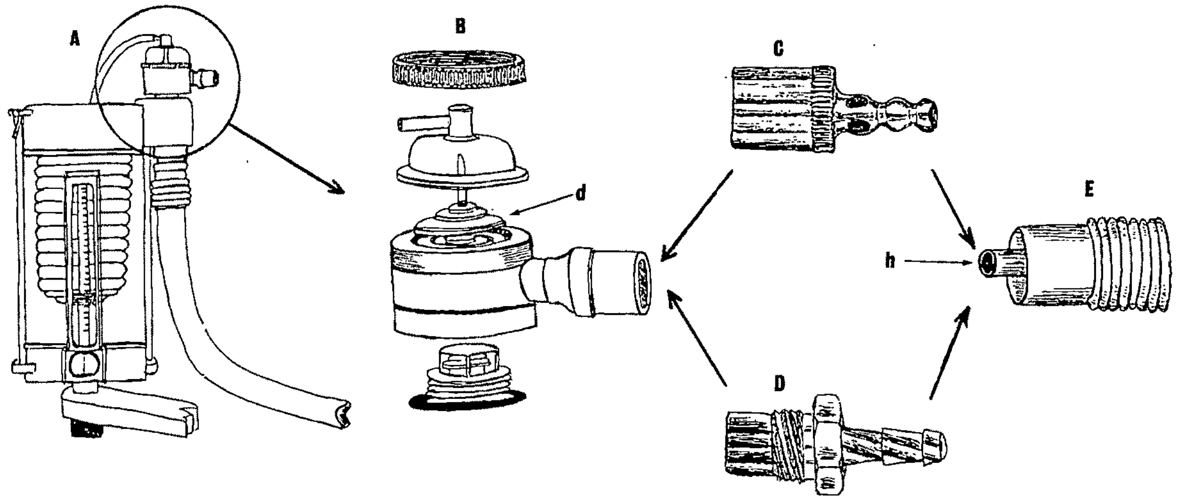

Figure. A, bellows assembly of Foregger 910 ventilator; B, exploded view of ventilator valve with rubber diaphragm (d); C, ported host adaptor, fashioned from a Foregger 15-mm Giuffre tube stop, which attaches to ventilator exhaust valve port; D, unported 15-mm hose adaptor which was inadvertantly attached to the ventilator exhaust valve port; E, scavenger system hose assembly with: central hose (h) which connects directly to the operating room suction system distally and to the ported hose adaptor (C) proximally; an outer, large lumen tube which is open ended distally and connects to the ventilator exhaust valve port proximally; d, rubber diaphragm of one-way exhaust valve which collapsed when negative pressure was applied by the central suction hose (h) through an unported hose adaptor (D); h, central hose in tube within a tube scavenging system.

In the case presented in this report, a subatmospheric scavenging system was connected to the exhaust port of the anesthesia ventilator (A in Fig). The system employed in our hospital consists of a tube within a tube arrangement.[5] A narrow inner hose connects a ported ventilator exhaust valve adaptor to the operating room central suction pipes (C in Fig). This is surrounded by a larger lumen corrugated tube which is attached to the ventilator exhaust port. The larger tube is open ended, approximately 5 feet from the exhaust port. Suction is constantly applied to the system through the inner hose. A ported hose adaptor must be used for connection of this inner host to prevent the build up of negative pressure. This interface was designed at our institution using connectors which were on hand (C in Fig). The larger outer hose acts as a ballast device to contain the gases which are rapidly exhausted during the expiratory phase of the ventilator. These gases are effectively scavenged during the inspiratory cycle of the ventilator when the exhaust valve is closed and the suction is applied entirely to this outer tube through the ported exhaust valve adapter. In this particular anesthesia ventilator, a diaphragm-type of one-way valve (B in Fig) was employed in the outflow tract. When the negative pressure was connected, a host adapter without relief ports (D in Fig) was incorrectly introduced into the system. As a result, the diaphragm valve (d in Fig) collapsed. This prevented the exhaust of gases from the anesthesia system. In a very short period of time, the positive pressure within the system became sufficient to cause the development of bilateral pneumothorax. This complication would not have occurred if a scavenger hose adapter with relief ports (C in Fig) for pressure equalization had been used. Use of the correct hose adapter, however, cannot guarantee that the same problem will always be prevented. Obstruction of the relief ports always remains a possibility. To obviate the problem of excessive positive or negative pressure, consideration might be given to the use of a pressure relief device within the anesthesia circle independent of the ventilator.

With the introduction of new and more sophisticated equipment, the administration of anesthesia has become more complex. The modification of preexisting equipment in order to meet new standards provides the opportunity for mishaps such as the one described in this report. As a result, the possibility of equipment malfunction resulting in patient harm is ever increasing. In spite of improved monitoring, direct observation and attention to detail by the anesthesiologist remain the most important factors in minimizing untoward incidents during anesthesia.

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Combined Nitroprusside-Dopamine Therapy

To assess the circulatory effects of afterload reduction and inotropism individually and in combination as rational therapy for refractory heart failure, nitroprusside and dopamine were administered to 13 patients with severe cardiac decompensation. Dopamine at average doses of 3 and 7 μg/kg/min produced increases in cardiac output and reductions in peripheral resistance. At doses of 15 μg/kg/min, dopamine increased heart rate, peripheral arterial pressure, and also side effects. Nitroprusside alone decreased left-sided filling pressures and increased cardiac output. When the agents were administered together, the increases in cardiac output were significantly greater than with either agent alone and there was physiologic improvement in overall circulatory function. The relations among changes in afterload (systemic impedance), preload (filling pressures), and cardiac index help to explain the salutary effects of combined therapy in patients with refractory heart failure. *(Stemple DR, Kleiman JH, Harrison DC: Combined nitroprusside-dopamine therapy in severe chronic congestive heart failure: dose-related hemodynamic advantages over single drug infusions. Am J Cardiol 42: 267–275, 1978)*

Labor and Delivery in the Eisenmenger Syndrome

The Eisenmenger syndrome carries a high mortality rate in women during delivery and the immediate postpartum period. It has been suggested that marked changes in shunt flow and pulmonary hemodynamics may be responsible. These functions were studied under various physiologic and pharmacologic conditions during labor and delivery in a patient with the Eisenmenger syndrome. Uterine contractions were associated with a decrease in the ratio of pulmonary to systemic blood flow (Qp/Qs) from 1.58 to 1.05. The Qp/Qs ratio also decreased (to 0.83) when forceps were applied during uterine contractions. Epidural anesthesia, oxytocin, and the supine position did not adversely affect pulmonary hemodynamics or shunt flow. On the basis of these results, if pregnancy cannot be terminated in a patient with the Eisenmenger syndrome, it is recommended that the patient be given high concentrations of oxygen and epidural anesthesia and that serial arterial blood gas determinations be performed to detect changes in shunt flow. *(Midwall J, Jaffin H, Herman MV: Shunt flow and pulmonary hemodynamics during labor and delivery in the Eisenmenger syndrome. Am J Cardiol 42:299–303, 1978)*

ANESTH ANALG
58:150-151, 1979

Convulsions Secondary to Intravascular Phenol: A Hazard of Celiac Plexus Block

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The efficacy of celiac plexus neurolytic blocks for pain of visceral malignancy is well documented.[1] Since these nerves are usually located in a vascular area, the possibility of intravascular injection is always present. The following case report deals with such an event.

Report of a Case

A 58-year-old man was admitted because of generalized abdominal pain from recurrent carcinoma 9 months after resection of an esophagogastric carcinoma. His pain was refractory to treatment with narcotic analgesics and he was referred to our pain service. He had no previous history of convulsive disorders. After evaluation, a differential epidural block was performed using a catheter. Based on the patient's own estimate, there was about 40% improvement with a placebo injection using 2 ml of normal saline. Residual pain was then completely abolished by 20 ml of 0.25% bupivacaine. Pain relief was complete for 2 hours after the sensory effects of the bupivacaine were gone, suggesting a sympathetic pathway for the patient's pain. A repeat block with 0.25% buipvacaine done 2 days later resulted again in complete pain relief. Both blocks were performed uneventfully without adverse reactions. The patient was then scheduled for a celiac plexus block with phenol under fluoroscopic control.

For the celiac plexus block, an intravenous infusion was begun and the patient put in the prone position. The technique as described by Bonica[2] was performed. With the tip of the needle in place, the patient was placed in the lateral position. Fluoroscopy in this position showed the tip of the needle to be about 1 cm anterior to the superior border of L_1. Twelve milliliters of contrast material were injected and there was diffusion of the drug at the area. The patient was repositioned prone. Repeat fluoroscopy showed the needle to be in the midline.

After negative aspiration, 10 ml of freshly prepared 6% phenol were injected. The patient immediately complained of ringing of the ears but this abated after 3 minutes. A repeat aspiration was negative and another 10 ml of 6% phenol was injected with the needle in the same position. Within 30 seconds of the termination of the second injection, the patient developed generalized seizure activity. He was rapidly turned to the supine position. Oxygen was given via an Ambu bag. Unresponsive for only a few seconds, the patient rapidly regained consciousness while the clonic activity was taking place and was able to communicate despite the convulsive motions. There was no tongue biting, frothy saliva at the mouth, or urinary or fecal incontinence. Respirations were adequate and the patient was not cyanotic prior to or following oxygen administration. The seizure activity ceased after 2 minutes. He was taken to the recovery room. There was no mental confusion, headache, or nausea immediately after the episode. His pain was still present the next day, but less intense. Two days later, the pain had increased to its usual severity. A repeat celiac plexus block was performed under fluoroscopy 2 days later using 20 ml of 6% phenol. A successful sympathetic block was obtained, as judged by postural hypotension and symptoms of hyperperistalsis, but pain relief was only partial. A percutaneous epidural neuroelectrode was later implanted and gave additional pain relief. A permanent subcutaneous receiver was implanted 3 days later. The patient's pain decreased to tolerable levels but was never completely abolished. He was discharged with a transepidural nerve stimulator in place.

Discussion

The lytic effect of phenol on nerves has been ascribed to a temporary anesthetic-like effect and to tissue destruction. This neurolytic action has been demonstrated to be nonselective, affecting fibers of all sizes.[3,4]

Accidental intravascular administration of phenol results in central nervous system stimulation manifested by muscle tremors and convulsions followed by depression.[5] The convulsant action of phenolic compounds was first demonstrated in cats in 1936.[6] Although the mechanism for this action is unknown, an effect on transmitter release appears to be involved. Phenol has been found to increase the amount of acetylcholine released by a single nerve impulse[7] while not altering the sensitivity of the end-plate to acetylcholine. The increase in transmitter release could facilitate central synaptic transmission,[8] resulting in neuronal hyperexcitability and convulsions.

The most striking characteristic of the convulsion in this patient was the almost complete absence of unconsciousness, despite the continued clonic motions of the convulsion.

Precise needle placement and meticulous attention to detail are necessary to prevent intravascular injections. During our second injection, the tip of the needle must have been within a vascular wall and then entered the lumen during injection. Aspiration midway through the injection might have led to recognition of the malposition of the needle tip.

ACKNOWLEDGMENT

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CVP versus PCWP

Both central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) have been used as guides to fluid replacement in patients undergoing abdominal aortic surgery. To test the hypothesis that changes in PCWP (ΔPCWP) may be reliably estimated from changes in CVP (ΔCVP), simultaneous measurements (302 paired observations) of CVP and PCWP, as well as of cardiac output, were made before and during operation on 55 patients. The correlation between ΔCVP and ΔPCWP was high ($r = 0.716$, $p < 0.001$). The estimated slope for the linear regression was 0.88. There were five patients who each had a low and falling CVP accompanied by a stable cardiac output and a rising PCWP; for them, a decision to administer fluid based on the CVP might have resulted in pulmonary edema. Although ΔCVP accurately predicted direction and magnitude of ΔPCWP in the majority of patients (90%), there was a small group in whom there was no substitute for direct measurement of PCWP. *(Rice CL, Hobelman CF, John DA, et al: Central venous pressure or pulmonary capillary wedge pressure as the determinant of fluid replacement in aortic surgery. Surgery 84:437-440, 1978)*

ANESTH ANALG
58:152, 1979

A New Complication Associated with the Use of Wire-Reinforced Endotracheal Tubes

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Lawrence G. Kushins, MD,‡

Ng and Kirimli[1] recently reviewed the hazards encountered in using anode endotracheal tubes. We experienced a complication not included in their paper and, to our knowledge, not reported previously.

Case Reports

Case 1

A 56-year-old man was to undergo surgical removal of a posterior fossa tumor. Since surgery was to be performed with the patient in the sitting position, we elected to use a wire-enforced anode endotracheal tube. After induction of anesthesia with thiopental sodium and of muscle relaxation with succinylcholine, a 7-mm (30 F), silicone-rubber, Surgitek wire-reinforced endotracheal tube (Medical Engineering Corporation) was placed in the trachea under direct vision. To aid in this maneuver, a bare, copper-wire stylet had been placed within the endotracheal tube. When the stylet was withdrawn, its rough, metal tip caught the wire spring of the tube and caused it to unravel and to be partially withdrawn from the open end of the endotracheal tube (Figure). Since the protruding wire prevented the attachment of the endotracheal tube to the circle absorber system, the entire assemblage (tube, wire, and stylet) was removed from the patient. Another anode tube without a stylet was placed successfully in the trachea and the remainder of the operation proceeded without incident.

Case 2

A 25-year-old man who had sustained thermal burns on his anterior chest was to have a split-thickness skin graft. Since the donor skin sites were on his back, a portion of the graft was performed with the patient in a prone position. After an intravenous injection of thiopental sodium, anesthesia was induced with halothane and nitrous oxide. A 6-mm (25 F), silicone-rubber, Surgitek wire-reinforced endotracheal tube was placed in the trachea under direct vision. When the bare, copper-wire stylet was withdrawn, its metal tip caught the internal spring of the tube and caused it to unravel and be partially withdrawn from the endotracheal tube. The tube was removed and a similar one placed without difficulty after the stylet was coated with local anesthetic jelly. The remainder of the operation proceeded without incident.

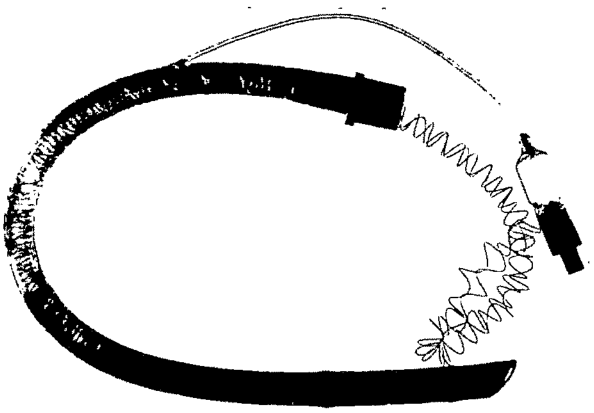

FIGURE. Wire-reinforced endotracheal tube used in case 1 with the internal wire withdrawn from the lumen by a metal stylet.

Discussion

Silicone-rubber, wire-reinforced endotracheal tubes are made in layers. The wire is embedded by repeated coatings of liquid silicone which solidify. The complication described in these two cases apparently occurred when the rough end of a copper stylet snagged the wire spring and pulled it from the tube. We sectioned and carefully inspected several Surgitek tubes and found the internal lining of the tube covering the wire to be very thin. The thinness of the internal surface also was confirmed by electrical means. When a copper stylet was connected through an electrical conductance meter to the wire and passed over the tube, much greater conductance was observed between the stylet and the internal surface as compared to the stylet and the external surface. This evaluation also showed that all the wire coils were covered by silicone-rubber and that the tubes were not defective. It seems likely that a stylet easily might snag the wire through this thin covering, particularly if the tube were damaged by prior use or a cleaning brush. This complication could have been avoided if a plastic covered or smooth tipped stylet had been used. Fortunately, no injuries occurred to our patients, but any difficulty with equipment that delays the establishment of an adequate airway is potentially hazardous.

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ANESTH ANALG
58:153-154, 1979

Hemoptysis Associated with the Use of a Flow-Directed Catheter

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The introduction of flow-directed, balloon-tipped pulmonary arterial catheters has made possible measurement of central venous pressure, pulmonary arterial pressure (PAP), and pulmonary-capillary wedge pressure (PCWP) before, during, and after anesthesia and surgery. Complications, including intracardiac knotting,[1] inadvertent snaring[2] in the right atrium, have been reported. Perforation of the pulmonary artery with[3] and without[4] hemoptysis has also been reported in patients with pulmonary arterial hypertension. The present case report records an instance of perforation of the pulmonary vasculature associated with the use of a flow-directed catheter in a patient without pulmonary hypertension.

Report of a Case

A 56-year-old man was hospitalized because of chest pain. Coronary angiography revealed 90% occlusion of the left anterior descending, 80% occlusion of the circumflex, and 85% occlusion of the right coronary arteries. Left and right heart hemodynamics and pressures were normal. Preoperative x-ray was not remarkable. The patient was scheduled for triple coronary artery bypass grafts.

Premedication consisted of morphine (10 mg) and scopolomine (0.4 mg) intramuscularly 1 hour before induction of anesthesia. A 20-gauge plastic cannula was inserted into the radial artery for the monitoring of arterial pressure and measurement of blood gases. A #7 Swan-Ganz catheter was inserted percutaneously under local anesthesia into a distal pulmonary artery via the right internal jugular vein for measurement of the pulmonary arterial pressure, wedge pressure, and cardiac output. After the right atrium was entered, the balloon was inflated with 1.5 ml of air. Pressure wave forms typical of first the right ventricle and next the pulmonary artery were obtained. The catheter was then advanced into a distal pulmonary artery to obtain wedge pressure. The diameter of this branch probably was not smaller than 13 mm (diameter of the balloon with 1.5 ml of air) because less than 1.5 ml of air did not occlude the pulmonary artery. The balloon was then deflated and the catheter irrigated. At this time pulmonary arterial pressure (PAP) was 30/15 mm Hg and pulmonary capillary wedge pressure (PCWP) 8 mm Hg; the catheter had been inserted 70 cm.

Anesthesia was then induced with diazepam (10 mg) and thiopental (200 mg) and maintained with morphine sulfate (1.5 mg/kg) and $N_2O:O_2$ (50:50). Muscle relaxation was achieved with pancuronium bromide and ventilation was mechanically controlled. After a sternal splitting incision, the chest was entered and a one-stage venous return cannula was inserted into the inferior vena cava through the right atrium. At this time PAP and PCWP had not changed significantly from preoperative values. Ten minutes later, after the manipulation of the heart began, PAP and PCWP were still the same but only 1 ml of air was required to occlude the pulmonary artery. Immediately after deflation of the balloon, bright red blood appeared in the endotracheal tube. The Swan-Ganz catheter was then withdrawn 5 cm. In 5 minutes approximately 150 ml of blood was suctioned through the endotracheal tube. Bleeding gradually subsided over the next 10 minutes. PAP did not change. No attempt was made to obtain wedge pressure during the remaining 3 hours of surgery. A chest x-ray taken in the intensive care unit 4 hours after the incident revealed no significant change in the lung.

Discussion

A Swan-Ganz catheter may migrate into one of the small pulmonary artery branches during manipulation of the heart even with the balloon deflated. Despite continuous monitoring, migration of the catheter may not be recognized because a small branch may still produce pulmonary artery wave forms. When the internal jugular route is used for insertion of the catheter, the tip of the catheter is usually in the wedge position after being inserted about 45 to 50 cm. Occasionally, however, the catheter is inserted 60 to 70 cm, as in our case. This "excess" length is curled in the right ventricle and with surgical manipulation of the heart, the distal end of the catheter may be forced into smaller vessels. If the balloon is then inflated to its normal size, tearing of the vessel wall and the wall of adherent lung tissues (alveoli) could occur and bleeding into the tracheobronchial tree would result. In our case, repeated attempts to obtain wedge pressure were not successful until 70 cm of the catheter had been inserted. Before the bleeding occurred, the balloon was inflated with only 1 ml of air. It is possible that even with 1 ml of air a distal thin walled vessel was torn. If bleeding occurs, the catheter should be withdrawn a few centimeters and not reinflated. This simple measure will probably prevent further damage of the injured vessels.

The exact cause of the hemoptysis was not apparent in the present case. Either a dilated bronchial vein or a small pulmonary artery branch might have been ruptured by the inflation of the balloon. Since the patient was breathing 50% oxygen at the time, the bright red color may have been due to rapid saturation of the blood in the endotracheal tube.

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It has been suggested that excessive balloon inflation might result in rupture of a distal pulmonary artery segment, particularly when severe pulmonary hypertension exists.[3] In our case, however, hemoptysis occurred without pulmonary hypertension despite cautious inflation of the balloon below capacity. When an excess of catheter has been introduced to obtain wedge pressure, the balloon should be inflated slowly with constant monitoring of the pulmonary artery pulse wave. When less than the recommended amount of air produces a wedge reading, the catheter should be withdrawn until the proper amount of air is necessary to occlude the artery.

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Neonatal Effects of Anesthesia for Cesarean Section

The Scanlon Group of Early Neonatal Neurobehavioral Tests (E.N.N.S.) was administered to 150 babies delivered by elective cesarean section. Fifty mothers received thiopental, 4 mg/kg, for induction of general anesthesia and 50 received ketamine, 1 mg/kg. A third group of 50 mothers received spinal anesthesia with tetracaine. Mothers receiving spinal anesthesia were given 100% oxygen by a transparent face mask and those undergoing general anesthesia received N_2O-O_2 (6 L:6 L) until delivery of the baby. All mothers were healthy and all babies weighed 2,500 g or more, were apparently normal, and had Apgar scores of 7 or more at 1 minute to a score of 10 at 5 minutes. Spinal anesthesia was associated with the greatest percentage of high scores on both the 1st and 2nd day for overall assessment, pinprick response, tone, rooting, sucking, Moro response, placing, alertness, and total decrement (habituation) scores. There was a statistically significant difference between all the scores for the spinal group compared to the other two groups. The scores were lowest following thiopental induction and intermediate with ketamine, although the difference did not reach statistical significance. *(Hodgkinson R, Bhatt M, Kim SS, et al: Neonatal neurobehavioral tests following cesarean section under general and spinal anesthesia. Am J Obstet Gynecol 132:670–674, 1978)*

ANESTH ANALG
58:155, 1979

An Aid to Rapid Intravenous Infusion

L. Brian Ready, MD, FRCP(C)*

Operating room anesthesiologists frequently encounter situations requiring the rapid administration of large volumes of intravenous fluids. The rate of infusion of blood or other fluids packaged in a collapsible bag can be increased with the application of external pressure to the bag by means of a "blood pump." Typically, these devices are inflated manually. The external pressure is indicated on a manometer. As the fluid content of the bag decreases, the external pressure—and thus the infusion rate—is reduced. This can occur quickly with the rapid infusion rates possible through large bore intravenous catheters. Frequently, rapid infusions are needed during periods of emergency when the anesthesiologist already has a multitude of functions to perform. A means of maintaining a rapid infusion rate without the need for repeated manual inflation of a blood pump is therefore desirable.

The figure indicates the application of a pressure-compensating automatic tourniquet to maintain constant pressure on the blood pump. The unit illustrated is the Kidde model 400 automatic tourniquet charged with dichlorodifluoromethane. The setup works equally well with automatic tourniquets powered by compressed nitrogen (such as the Zimmer Inflato-Matic). The blood pump illustrated is manufactured by Fenwal.

Once an intravenous route has been established, the manual inflating bulb is simply removed from the blood pump and the tubing leading from the automatic tourniquet attached in its place. The maximum recommended inflating pressure of 300 torr is selected and the blood pump inflated. Thus, a constant infusion pressure is assured until the bag of fluid is empty. A 3-way stopcock is incorporated in the pressure line to permit rapid deflation and changing of fluid bags (500- or 1000-ml capacity) without further need to touch the automatic tourniquet. By attaching an additional length of tubing, the stopcock also facilitates venting of the expended dichlorodifluoromethane vapor to an anesthetic gas scavenger device. The system can be kept fully pressurized while using the clamp on the intravenous tubing to regulate flow if less than the maximum infusion rate is used. A Y-connector inserted in the pressure line permits simultaneous inflation of two blood pumps with a single automatic tourniquet.

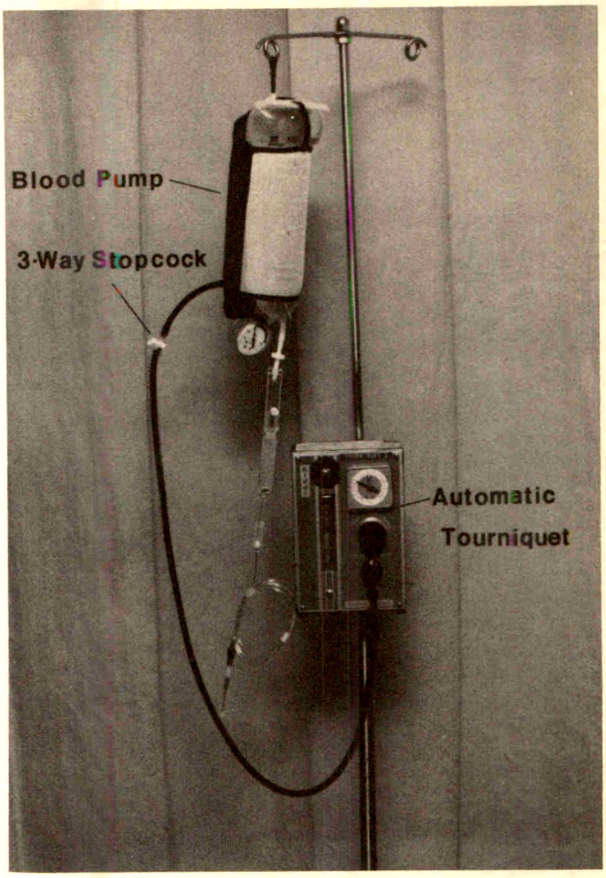

FIGURE. Setup for rapid intravenous infusion.

Since automatic tourniquets are found in most modern operating rooms, this aid to rapid intravenous infusion is available without the need to purchase further equipment. (A commercially available, spring-driven device manufactured by Tycos performs the same function, but this device is recommended for use only with 500-ml bags of fluid.)

This setup has also been suggested to a number of orthopedic surgeons who now use it to pressurize their irrigation solutions during arthroscopy.

In summary, an automatic tourniquet can be employed to pressurize a blood pump when rapid intravenous infusion is necessary.

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letters TO THE EDITOR

Bottle Adaptors for Vaporizers

To the Editor:

The report by Klein and Camenzind[1] of "Hazard of Bottle Adaptors for Vaporizers" is disturbing. The keyed filler system concerned was designed to prevent just such accidents. If all suppliers of volatile anesthetic agents would fit the keyed collars to their bottles, then such confusion would be prevented mechanically.

It is doubly unfortunate that not only did this supplier of halothane not fit the keyed collar to the bottle, but in addition, they printed the label with an orange band which users have come to associate with enflurane. A proposed international standard for Keyed Filling Devices for Liquid Anesthetic Vaporizers, and the Canadian National Standard Z1168.4 both include a list of recommended colors for the bottle adaptors.

The colors recommended are:

Halothane—red (Pantone[2] 200, Munsell[3,4] 5R 4/14),
Enflurane—orange (Pantone 144, Munsell 2.5YR 6/16),
Methoxyflurane—green (Pantone 334, Munsell 10G 5/10),
Isoflurane—white.

To explore this reported problem, a meeting was held on October 25th in Chicago; it was attended by Dr. Klein, most distributors of the volatile agents concerned, the manufacturer of this keyed filling system, and manufacturers of other vaporizers.

It is clear that if agreement can be obtained of all suppliers to use the keyed bottle collars and adopt the recommended standard colors, such potentially lethal mistakes can be eliminated, at the cost to the user of a few cents per bottle.

All suppliers of volatile liquid anesthetics will, on request, supply their agents with bottles fitted with the index collars which will mechanically prevent such accidents. Anesthesiologists are urged, therefore, to insist that their hospitals' purchasing departments specify that these collars be fitted, when they place the orders.

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4. Munsell System of Color Notation, Munsell Color Division, Kollmorgen Corp, Baltimore, MD 21218

Swallowing an Endotracheal Tube

To the Editor:

Mitchell et al in their recent article (Anesth Analg 57:590–591, 1978) stated that they believed theirs was the first documented case of the swallowing of an endotracheal tube in a newborn.

Dickson and Fraser[1] reported five such cases in 1967. This was followed by two case reports.[2, 3] Two more cases were reported in 1970.[4, 5]

This complication can be prevented by using a connector that fits firmly into the endotracheal tube. However, if the tube is swallowed, resuscitation should continue without interruption. When the patient's condition has stabilized, the tube may be removed.

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Renal Perfusion, Mannitol, and Nitroprusside

To the Editor:

In their recent publication, Drs. Behnia, Siqueira, and Brunner stated that they "observed no significant change in urine P_{O_2} during hypotension" induced in patients by sodium nitroprusside infusion.[1] They anticipated that "reduced renal perfusion during hypotension would reduce O_2 supply to the kidney, thereby reducing medullary tissue O_2 tension and hence urine P_{O_2}."[1] Their unexpected finding is likely due to a change in renal blood flow as a result of the mannitol infusions which their patients received before and throughout the hypotensive period.

It has been demonstrated that mannitol, an osmotic diuretic, reduces normal renal medullary hypertonicity.[2] This is accomplished in part by an increase in renal medullary blood flow induced by mannitol.[3] It has been shown that mannitol infusion in dogs results in increased total renal blood flow with proportional increases in both cortical and noncortical flow with a reduction in noncortical vascular resistance.[3]

In the presence of mannitol, the effect of sodium nitroprusside on renal blood flow and distribution may be altered. An increase in renal blood flow and a reduction in noncortical vascular resistance produced by mannitol would provide an explanation for the normal urine P_{O_2} observed during sodium nitroprusside-induced hypotension. This suggests that the effect of mannitol rather than sodium nitroprusside was being studied.

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To the Editor:

We thank Dr. Arnold Berry for his comment on our work. However, we believe that the observed urine P_{O_2} values were probably related to the sodium nitroprusside (SNP), not mannitol, since both control and hypotensive measurements were made during mannitol infusion. Mannitol may alter renal blood flow distribution but the mannitol effect, if any, would be present during the control as well as hypotension periods. We were looking for changes and each patient served as his own control. From this study in man without a comparison group with no mannitol infusion, a synergistic combined effect of mannitol with SNP cannot be ruled out. Our ongoing experiments in animals suggest that urine P_{O_2} during SNP-induced hypotension is similar to that without mannitol infusion.

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Gastric Acidity and Glycopyrrolate Premedication

To the Editor:

We read with interest the paper by Baraka et al (Anesth Analg 56:642–645, 1977). As we are also working on glycopyrrolate and have been doing similar work, we would like to point out some discrepancies in the above paper.

The doses of the two anticholinergics studied by Baraka et al, glycopyrrolate and atropine, are not comparable. Dose-response curves (Figure) derived from studies in volunteers[1,2] show that the antisialogogue activity of glycopyrrolate is 5 times that of atropine. It was thus not surprising that glycopyrrolate proved superior. Our own observations (to be published shortly) show that 0.2 mg of glycopyrrolate and 1.0 mg of atropine were indistinguishable regarding the effects on pH of gastric contents, though both are superior as compared to a control group.

The statistical tests used by Baraka et al, also appear to have been employed incorrectly. It is unacceptable to carry out the chi-squared test on percentages; rather absolute values must be analyzed. When this is done, atropine and glycopyrrolate do not show any significant difference. In any event many statisticians would suggest that due to the small number of patients, the Fisher's exact test would be more appropriate. Furthermore some of the mathematics used would appear to be erroneous. The table shows pH values for only 21 patients, 12 in the "less than 60 minutes" group and 9 (out of 11) in the "more than 60 minutes" group. The missing values for the two patients in the latter group are not given though the mean has been calculated for 11 patients, effectively deducing the pH values in those patients to be zero. This is obviously incorrect. The significant results have again been obtained by employing the percentages.

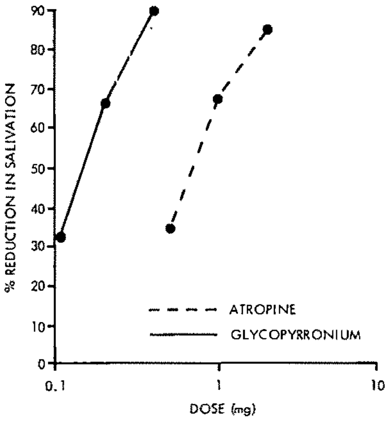

FIGURE. Dose response of atropine and glycopyrronium on salivary secretion.

The method of calculating mean pH by taking the pH values as ordinary numbers is again debatable. Should the mean pH not be obtained by first converting the individual pH values into the concentration of H$^+$ ions, getting a mean H$^+$ ion concentration and converting it back into pH?

Anticholinergic drugs like atropine have now been conclusively shown to reduce the opening pressure of the cardioesophageal sphincter.[3-5] This has been shown to be true for glycopyrrolate as well.[6] In addition, the anticholinergic drugs reduce the motility and perhaps delay gastric emptying. Increased intragastric pressure in parturient patients, in addition to the above mentioned factors will only increase the risk of aspiration. This is hazardous even if the contents are alkaline.

We believe that safety in obstetrics will really be achieved by administration of specific H$_2$-receptor inhibitors like cimetidine and by drugs which increase gastric emptying like metoclopramide.

Glycopyrrolate has a number of advantages over atropine, chief amongst these being good antisialogogue action, minimal cardiovascular effects, and lack of any central effects. These advantages should be exploited in routine anesthetic practice rather than the dubious and unproven attribute of raising the pH of gastric contents.

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To the Editor:

I have read the letter to the Editor by Doctors Mirakhur and Dundee and feel compelled to respond lest the misconceptions that result from their letter might adversely affect the anesthetic care administered to parturients in this country.

The misconception about the calculation of mean pH values has already been discussed in the editorial,[1] so I will not deal with that issue. However, the second misconception is a result of the statement that "the doses of the two anticholinergic drugs used are grossly incomparable." This statement is supported by the statement that follows, that "dose-response curves derived from studies in volunteers show that the antisialogogue activity of glycopyrrolate is 5 times that of atropine." First of all it is a well known fact that there are different degrees of resistance (to anticholinergic agents) at different parasympathetic endings.[2-4] For example, it is well established that the parasympathetics to salivary glands are affected by low doses of atropine while 2½ times these doses produce the same degree of inhibition of the cardiac vagus and 10-20 times these doses produce the same degree of inhibition of accommodation.[2,4] Therefore, even assuming that the antisialogogue activity of glycopyrrolate is 5 times that of atropine (and this is *not* the ratio reported by Wyant,[5] who found glycopyrrolate to have twice the antisialagogue activity of atropine), to assume that the same relationship holds for inhibition of gastric secretions, is fallacious. This is borne out by the fact that the authors of the letter to the Editor found 0.2 mg of glycopyrrolate to be indistinguishable from 1 mg of atropine *with respect to the effect on the pH of gastric contents*. Having obtained these results, these investigators must have asked themselves why glycopyrrolate was 5 times as potent an antisialogogue (when both drugs were given in their prescribed dosages), and yet was no more potent than atropine in raising the pH of gastric contents. The answer is clearly that the dose of glycopyrrolate was simply too low to achieve the desired elevation of pH. That such is the case was surely substantiated by the data presented by Baraka et al,[6] which indicated that 0.4 mg of atropine would elevate the pH of gastric contents to above 2.5 in 82% of the parturients *if* the glycopyrrolate was administered more than 60 minutes prior to the induction of anesthesia. Clearly, both dose and time of administration are important. As a matter of fact, Stoelting[7] recently also demonstrated that 0.2 mg of glycopyrrolate was too small a dose to elevate the pH of gastric contents significantly. In short, the findings of Mirakhur and Dundee that 2 mg of glycopyrrolate is indistinguishable from 1 mg of atropine regarding the effects on the pH of gastric contents, is simply a result of inadequate dosage, and does not indicate that glycopyrrolate, given in adequate dosage and a sufficient time prior to the induction of anesthesia (or sampling of gastric juice), cannot raise the gastric pH above 2.5 in a clinically significant percentage of cases.

The last misconception I would like to address is that which results from the statement that "we believe that safety in obstetrics will really be achieved by administration of specific H_2-receptor inhibitors like cimetidine and by drugs which increase gastric emptying like metoclopramide." At a recent meeting of the American Society of Anesthesiologists, I, too, went on record stating that the conquest of aspiration as a major, life-threatening complication of anesthesia, is just around the corner.[8] In a panel discussion I stated that this dreaded complication would one day be totally avoided, even in emergency cases, by the sequential administration of a gastric emptying drug, such as metoclopramide, a specific H_2-inhibitor, such as cimetidine, a potent long-acting anticholinergic, such as glycopyrrolate, and an antacid that would of itself not cause pulmonary problems if aspirated, *provided* these drugs were given in the proper dosage and in the proper time sequence. However, right now metoclopramide is not available to the American anesthesiologist, and the few studies carried out in this country to document its efficacy in emptying gastric contents have been disappointing (Personal communication, data on file at A. H. Robins Co.). Cimetidine, the only available specific H_2-receptor inhibitor, is not available in parenteral form and has not been approved for preanesthetic medication by our Food and Drug Administration, and while that does not absolutely prohibit anesthesiologists from using this drug in premedicating patients for surgical anesthesia, it certainly would be unwise, to say the least, to use it in premedicating obstetrical patients until the pharmacokinetics of the drug and the possible effects on the newborn have been studied. Furthermore, it is interesting to note that in a recent study of the efficacy of cimetidine in raising gastric pH to above 2.5, Stoelting[9] found that 84% of patients administered cimetidine, 300 mg, 90 minutes preoperatively, had gastric juice pH in the "safe range," i.e., above 2.5. Thus the degree of protection afforded by this "specific H_2-receptor inhibitor" is indistinguishable from that afforded by glycopyrrolate, 0.4 mg given 90 minutes preoperatively, as reported by Baraka.[5]

While no one has claimed glycopyrrolate to be a panacea, or even the final solution to the problem of aspiration, it is approved, it is available now in parenteral form, and it is the most effective agent that we have *today*. To deny patients its benefits until something better comes along would certainly not be in the best interests of our patients.

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Hypothermia and Pancuronium

In 14 cats given pancuronium, 120 μg/kg IV, neuromuscular block lasted between 2.5 and 3.0 times longer at 29 C than at 34 or 39 C. The apparent plasma elimination half-life was 46 ± 7 min (SE) at 29 C as compared to 21 ± 2 and 25 ± 6 min at 34 and 39 C, respectively. The volume of distribution of the central compartment and total volume of distribution at steady state were less at 29 and 34 C than at 39 C. Total plasma clearance was 4.3 ± 0.4 ml/kg/min at 29 C and 10.7 ± 0.9 and 10.9 ± 1.5 ml/kg/min at 34 and 39 C, respectively. The reduced plasma clearance resulted at least in part from a markedly reduced biliary and urinary excretion of pancuronium at 29 C as compared to 34 and 39 C. In four other cats, the plasma concentration of pancuronium was correlated with depression of twitch tension under steady-state conditions. The ED_{50} of pancuronium (plasma concentration required for a 50% depression of twitch tension) was 0.035 and 0.073 μg/ml at 29 and 38 C, respectively. The authors conclude that a pancuronium neuromuscular block is prolonged at 29 C because of an increased sensitivity of the neuromuscular junction to pancuronium and delayed biliary and urinary excretion. *(Miller RD, Agoston S, van der Pol F, et al: Hypothermia and the pharmacokinetics and pharmacodynamics of pancuronium in the cat. J Pharmacol Exp Ther 207:532–538, 1978)*

Effects of Packed Red Cells on Host Defense

Whole blood and packed red cells used for resuscitation of acute blood loss in dogs were compared with respect to a number of indices of host defense. Dogs subjected to a blood loss equal to 8% of body weight exhibited significant depression of serum protein, C3, IgG, and total opsonic activity when resuscitated with packed red cells in saline. No such depression in serum components or activity was observed in identically bled dogs resuscitated with whole blood. There were no differences in the rate of clearance of intravenously injected bacteria, indicating intact reticuloendothelial system (RES) function in both groups. These data suggest that whole blood may be preferable to packed cells for resuscitation of acute hemorrhagic shock when the effect on resistance to infection is considered. *(Beiting CV, Kozak KJ, Dreffer RL, et al: Whole blood vs packed red cells for resuscitation of hemorrhagic shock: an examination of host defense parameters in dogs. Surgery 84:194–200, 1978)*

book REVIEWS

The Caval Catheter, by C. Burri and F. W. Ahnefeld, New York, Springer-Verlag, 1978, 84 pp. $14.00.

This monograph, with 67 pages of text and 496 references, is purported by its authors to be an up-to-date survey of the state of the art of central venous system access. In this regard, the book did not fulfill my expectations and certainly does not cover the subject adequately.

The book is poorly organized with redundancies in many of the chapters. For example, the entire section on central venous system access in children is contained in the chapter on "Indications." Excepting the section on cutdowns, the content of chapter III is duplicated elsewhere in the book. There are numerous errors in syntax and the text is rambling and repetitive. The tables and graphic illustrations are frequently poorly labeled leading to reader inconvenience and confusion. (An example of such a poorly labeled illustration is figure 40 on page 51.) Additionally the authors subject the reader to continual annoyance by referring to illustrations many pages removed from that particular site of text. (The most blatant example is a reference on page 51 to figure 31 which appears nine pages earlier on page 42.)

With regard to content of the monograph, there are several significant deletions which skew the overall tenor of the book toward subclavian vein catheterization. It would appear that the authors of this text had never heard of the usefulness of the flexible angiographic wire catheter guide (J-wire or spring guide) as a valuable adjunct in facilitating the passage of a central venous catheter. The authors also neglected to mention, except in passing, the usefulness of the over-the-needle catheter apparatus, both for definitive and introductory central venous system cannulation. Reference to silicone elastomer as a catheter material of low thrombogenic potential was omitted. Technique descriptions left a great deal to be desired, in my estimation, and appeared to be directed toward the experienced surgeon. For example, the authors recommended the use of constant aspiration with a syringe to prevent air embolism recommended *only* for the infraclavicular approach to the subclavian vein. The use of an aspiration syringe should be standard procedure for all techniques, except those in the arm. Despite the fact that the authors ascribe almost 50% of catheter embolizations to severance of the catheter by the needle, recommendation of abandonment of through-the-needle catheters in favor of over-the-needle catheters was never mentioned.

The authors make a number of strong statements without documentation. An example of this is, "A proviso for successful puncture (of the internal jugular vein) is careful palpatory identification of the carotid artery."

Despite the previously mentioned deficiencies, the book does a reasonable job in reviewing the complications of caval catheterization (although misinterpreting some), and the section on dealing with catheter embolism is excellent. The section of recommendations (chapter IV) makes a number of good points.

The authors have neglected to include much available information regarding internal jugular vein cannulation. This represents a serious deficiency and because of this and many other shortcomings, I cannot recommend purchase of this book. This would especially hold true for an anesthesiologist attempting to learn about central venous system access from the beginning.

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Respiratory Function of the Lung and Its Control, by Fred S. Grodins and Stanley M. Yamashiro, New York, Macmillan Publishing Co., Inc., 1978, 141 pp. $13.50.

The reader of this short introductory textbook of respiratory physiology will learn from the first sentence of the first chapter that the general approach of the book is unique. "The overall behaviour of the respiratory system in man is an expression of the integrated interaction of many different unit processes." The traditional compartmental view of respiratory physiology is replaced by a 'systems analysis' approach, based on a division of the respiratory system into interacting unit processes. The unit processes identified include: pulmonary ventilation, pulmonary diffusion, blood chemical processing, circulation, tissue diffusion, and tissue metabolism. Furthermore, the respiratory system is seen as a 'metabolic servo-mechanism' designed to match pulmonary and metabolic gas exchange rates over a wide range without change in arterial composition. The description of the control component of the respiratory system is the portion of the text which readers will find differs most from traditional approaches.

How successful is the approach used? The preface states that the book evolved from lecture notes used in teaching respiratory physiology to students at various levels. I suspect that in the classroom, with the authors present to carefully lead the student through both the basic elements of respiratory physiology and the basic concepts of systems analysis, the approach provides an interesting and effective way to teach and learn respiratory physiology. However, I predict that the independent reader, who is a novice in both fields, will be more confused than assisted by this textbook.

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Biological Foundations of Biomedical Engineering, edited by Jacob Kline, Boston, Little, Brown and Co., 1976, 988 pp. $37.50.

This book is compiled from the course syllabus of "Unified Systems Approach to the Medical Sciences for Biomedical Engineers" at the University of Miami. It is divided systematically into eight parts addressing the basic sciences, the cardiovascular, respiratory, nervous, endocrine, gastrointestinal, and reproductive systems, and the body fluids. It has an index of 85 pages, enabling the reader to refer to any subject either from a physiologic, medical, or engineering standpoint. The contents refer mainly to normal physiology, with higher mathematical explanation for many of the phenomena. Readers who have allowed their knowledge of calculus and exponents to become rusty will find some sections difficult to assimilate.

Various subjects are dealt with in more than one section. It is intriguing to compare analyses of vascular impedance starting from either vascular resistance or velocity of phase change. The Starling-Landis hypothesis is given greater depth when considered by both cardiovascular and gastrointestinal experts. A section on acid-base balance perpetuates the lack of distinction between *acidosis* and *acidemia* and, therefore, the confusion of students who are new to the subject. The section on the reproductive system is both unique and outstanding. It covers the female reproductive system and the development of the human from ovulation to the neonatal period.

The perinatologist will find the analyses of placental and fetal circulation, fetal monitoring, and the changes that occur during labor and delivery concise, lucid, and valuable.

This book is an excellent companion for a course in biomedical engineering, and it is highly commended for resource material wherever physiologic studies are being done and in anesthesiology training programs.

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Positioning in Anesthesia and Surgery, by John T. Martin, Philadelphia, W. B. Saunders Co., 1978, 230 pp., $20.00.

This book presents 10 review chapters written in logical sequence by 16 well qualified anesthesiologists and surgeons.

In succeeding chapters the diversification of knowledge and experience becomes evident. The surgeon, knowing the best approach to a specific anatomical area, necessarily dictates the position of the patient. He is aware of the effects of positions that may adversely affect the patient and enhance the potential pathology of trauma and disease. The anesthesiologist through comparable training and experience seeks to place and adjust the patient in the necessary positions without compromising respiratory, circulatory, neurologic, or anatomical requirements. He must also utilize suitable anesthetic agents, techniques, and supportive therapy to maintain appropriate levels of anesthesia and relaxation for a satisfactory surgical field.

An excellent chapter reviews the physiologic variations in the normal conscious human patient subjected to change from the erect to the supine position. It serves as a basis of comparative values for problems encountered in the use of positions and their variations for the anesthetized patient. In succeeding chapters each fundamental position is considered in relation to its advantages and disadvantages, as well as its effects on respiratory, circulatory, neurologic, and other systems. Photographs, drawings, and instructions based upon experience promote the safe placement of the patient in each position with the appropriate use of pads, pillows, braces, headrests, and stirrups. There is pertinent commentary as to the results of each failure to place and maintain the patient in a safe position.

The last chapter reviews neurologic injuries associated with trauma, malposition, and inadvertent surgical trespass. Photographs, charts, and graphs identify the most common areas of neurologic involvement.

Overlap of information in succeeding chapters serves to emphasize the coordination of thought between surgeons and anesthesiologists. The literature has been well reviewed and the references are pertinent and updated. This book is recommended for young anesthesiologists and surgeons or those not experienced enough to have lived through the discomfort and stress involved in the results of malposition.

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Practical Anesthetic Pharmacology, edited by Rafik R. Attia and Alan W. Grogono, New York, Appleton-Century-Crofts, 293 pp., 1978.

The stated objective of this short volume is to serve as a "compact pharmacology text for the trainee and the practioner in anesthesiology." The editors have correctly identified an area of need in our pharmacologically based specialty. Where the text remains faithful to this well defined goal, the book addresses an important issue and serves a valuable purpose. Readily accessable within these 293 pages are concise descriptions of the clinical pharmacology of the medications which may be encountered in the perioperative period. The topics are well organized into 16 chapters, more than half of which are written by the two editors themselves. The remaining chapters, contributed by well known authorities in their respective areas, conform well to the style, and content, as set forth by the editors. Perhaps the strongest features of the book are the liberal use of clear and practical tables and charts, and extensive bibliographies which enhance each chapter.

The text bogs down only where it fails to resist the temptation to become too broad, to become all things to all readers. Several of the chapters are weakened by brief, superficial digressions into other disciplines (most notably physiology) which only serve to dilute what are, otherwise, solid and concise discussions. The editors would have done better to rigorously maintain "compactness" and confine the discussions to the topic at hand.

As billed in the title, this is a very practical textbook, authored and edited by anesthesiologists. As such, it should be a valuable addition to the bookshelf of any clinical anesthesiologist.

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International Anesthesiology Clinics Regional Anesthesia: Advances and Selected Topics, edited by M. d'A. Stanton-Hicks, Boston, Little, Brown and Co., 1978, 204 pp.

Owing to greatly refined analytical techniques, the first four chapters of this truly international volume bring to regional anesthesia the solid scientific basis established a decade ago for general anesthesia. Technical advances introduced by the newer long-acting local anesthetics are nicely summarized by Covino. The chapter on local anesthetic kinetics brings perspective to "continuous" blocks, though the general reader may find the mathematics heavy going. The chapter on fetal effects of local anesthetics nicely blends laboratory and clinical studies; even relatively low blood levels of local anesthetics affect the fetus in subtle ways that are just beginning to be explored.

The remaining 100 pages deal selectively with four major areas of regional anesthesia: peridural, intercostal, sympathetic, and upper arm blocks. Although all are of high quality, Boas' chapter on sympathetic blocks is so complete as to be a virtual "mini-course." The anatomical sketches in the Editor's chapter on epidural anesthesia are of unusually fine quality; I recommend them to instructors.

By selecting topics that have reached a certain maturity, the danger of instant obsolescence has been minimized. Theory and hard data are lucidly presented, the two are never confused, and the reader is clearly shown where the gray areas of doubt lie. By presenting a few topics in depth, the volume succeeds in conveying the spirit of the field to the novice while offering valuable international reference material to the specialist.

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Adverse Response to Intravenous Drugs, edited by J. Watkins and A. M. Ward, New York, Grune & Stratton, Inc., 1978, 188 pp., $17.00.

This book is based in large part on a symposium held in June 1977 at the University of Sheffield Medical School. The material presented at the symposium was edited, expanded, and supplemented to produce a small treatise that provides a broad overview of the spectrum of adverse reactions to intravenous drugs. Special emphasis is placed on adverse reactions to intravenous anesthetics, muscle relaxants, and plasma expanders. Detailed chapters discuss the pharmacokinetics of an intravenous bolus, define the incidence and causes of both local and systemic adverse reactions, summarize the systemic reactions to plasma substitutes, discuss the immunologic aspects of hypersensitivity, and discuss histamine- and nonhistamine-mediated reactions. Shorter chapters on specific drugs and management supplement the longer chapters.

The book is well edited and the material presented in a uniform style of writing. Adverse drug reactions are either increasing in incidence or our awareness of these adverse reactions is increasing. This book can provide the knowledge needed to evaluate the causal mechanisms of an adverse reaction critically, to evaluate the test patients who have had remote adverse reactions, and to treat adverse reactions properly. An extensive current bibliography is provided for each chapter.

Enlargement of several of the chapters, particularly the one on management of acute anaphylaxis, would augment the utility of this book as a reference source. In addition, the focus on reactions to drugs and plasma substitutes not available in the United States (e.g. Althesin) detracts somewhat from its appeal to American readers. However, this well organized and well referenced book should be a welcome edition to a teaching department's library.

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BOOK NOTES

A Practice of Anaesthesia, Fourth edition, by H. C. Churchill-Davidson, Philadelphia, W. B. Saunders Co., 1978, 1542 pp., $65.00.

The new edition of this textbook is a pleasant reminder of the advances that have occurred in our specialty during the past few years. The general appearance of the book is very similar to that of the third edition, but the list of associate and assistant editors has been extensively revised. Rather than just add new material to old, the editors and authors have reorganized the text, combined chapters, and deleted as well as added new subject matter and graphics. The result is that almost every page has changed from the previous edition and a new current reference book has replaced the aging third edition, while still retaining its basic characteristics.

Since this book was first introduced in 1960, it has gained worldwide popularity and is now available in five languages. The all-English staff of editors and assistants have reached beyond the British Empire by including much material from outstanding journals around the world.

The book would make an excellent addition to the library of any student of anesthesia; ownership of an earlier edition should be considered as a contraindication to purchasing this volume.

Drugs in Anaesthetic Practice, Fifth edition, by M. D. Vickers, F. G. Wood-Smith, H. C. Stewart, Woburn, MA, Butterworth & Co., 1978, 604 pp., $29.95.

Although this British book contains a number of additions to and deletions from previous editions, perhaps the most important change is the inclusion of some alternate names for the drugs taken from the United States Pharmacopia, National Formulary, and United States Adopted Name. These American names are not indexed; however, the appendix is most helpful in the translation of trade names, both British and American, to scientific names that are approved on both sides of the Atlantic.

BOOKS RECEIVED

Handbook of Blood Pressure Monitoring, by Bruner JMR, Littleton, MA, PSG Publishing Co, Inc, 1978

Surgery of the Neonate, by Coran AG, Behrendt DM, Weintraub WH, Lee DC, Boston, Little, Brown and Co, 1978, 272 pp, $32.50

Monitoring Surgical Patients in the Operating Room, by Gravenstein JS, Newbower RS, Ream AK, Smith NT, Barden J, Springfield, IL, Charles C Thomas, Publishers, 1979, 270 pp, $22.50

Epidurography: A Diagnostic Aid in Spinal Lesions, by Gupta RC, Allahabad, India, Bhargava and Co, 1978, 83 pp

Why Not Say It Clearly, by King LS, Boston, Little, Brown and Co, 1978, 186 pp, $5.95

The Chemistry of Human Behavior, by Meltzer HL, Chicago, Nelson-Hall Publishers, 1979, 261 pp, $17.95

Stress-Free Anaesthesia, by Royal Society of Medicine, New York, Grune & Stratton, Inc, 1978, 98 pp, $10.25

Mechanical Misadventures in Anaesthesia, by Wyant GM, Buffalo, NY, University of Toronto Press, 1979, 174 pp, $15.00

A Guide for Authors

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Title page. Make the title concise. Avoid "Effect of" and similar noninformative phrases. List author's name(s) and degrees (title and affiliation should be cited in footnote to name). Restrict the number of authors to those making contributions. The senior author will be asked to justify the inclusion of more than four co-authors. Include on the title page: department and name and address of institution where research was performed; sources of support (if any); and name and address of the individual to whom reprint requests are to be addressed. Use double spacing throughout.

Abstract. On a separate page present a complete yet brief synopsis of what was studied, why it was studied, what the results were, and what the conclusions are. Use double spacing. Do not exceed one page. The Abstract is page 1. Case reports and review articles do not need abstracts but instead should conclude with brief summarizing paragraphs.

Text. Original articles contain four parts: Introduction; Methods and Material; Results; and Discussion. The start of the Introduction is page 2; number all following pages sequentially. Conclude the Discussion with a paragraph summarizing conclusions.

Abbreviations. Define all abbreviations except those approved by the International System of Units for amount of substance, mass, length, time, temperature, electric current, and luminous intensity. Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

Symbols. Define all symbols when first used. Respiratory symbols must follow Pappenheimer J, et al: Standardization of definitions and symbols in respiratory physiology. Fed Proc 9:602–605, 1950.

Drug names. Use generic names. Brand names, when used, appear in parentheses following generic names

Units of measurement. Use only terms approved by the International System of Units, e.g. meter, kilogram, and liter, for length, mass, and volume, respectively. Report concentrations and amounts of substances in molar units (e.g. moles per liter), not in mass units (milligrams percent) when feasible; when not feasible, give both. Report partial pressures in mm Hg or torr. See Young DS: Standardized reporting of laboratory data. N Engl J Med 290:368–373, 1974.

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Munson ES, Embro WJ: Enflurane, isoflurane, and halothane and isolated human uterine muscle. Anesthesiology 46:11–14, 1977

Book

Avery MA, Fletcher BD: The Lung and Its Disorders in the Newborn Infant. Third edition. Philadelphia, WB Saunders Co, 1974, pp 54–58

Chapter in Edited Book

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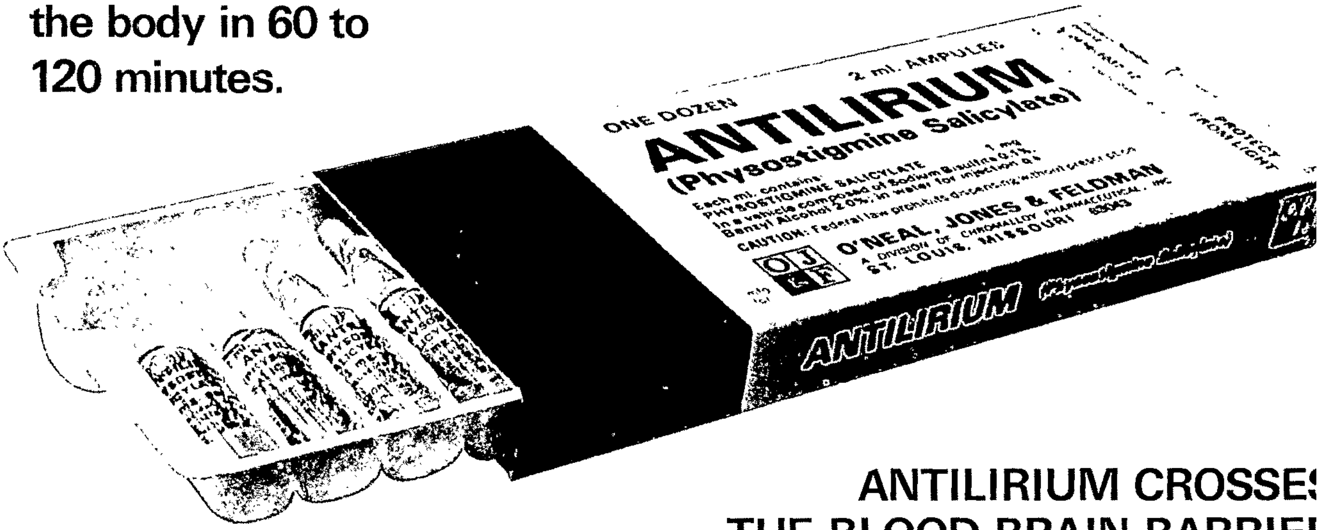

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ANTILIRIUM, unlike other anticholinesters including neostigmine does not have a quaternary nitrogen atom, but has a tertiary amine. For this reason it is nonionized and rapidly crosses the blood brain barrier

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ANTILIRIUM

(Physostigmine Salicylate)

DESCRIPTION: ANTILIRIUM Injection (physostigmine salicylate) is OJF's brand of physostigmine salicylate.

ANTILIRIUM INJECTION 1 mg./ml.
FOR INTRAMUSCULAR OR INTRAVENOUS USE
Each ml. contains:
PHYSOSTIGMINE SALICYLATE 1 mg.
In a vehicle composed of Sodium Bisulfite 0.1%, Benzyl Alcohol 2.0%; in water for injection q.s.

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. The action of acetylcholine is normally very fleeting because of its hydrolysis by a specific enzyme. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine. The changes in body function which are produced by the injection of physostigmine are, therefore, very similar to those which would occur from simultaneous stimulation of the parasympathetic nerves and include contraction of the pupil, increased tonus of the intestinal musculature, constriction of the bronchi and stimulation of secretion of the salivary and sweat glands.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quarternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Drugs with anticholinergic properties primarily antagonize acetylcholine competitively at the neuroreceptor site. Cardiac muscle, exocrine glands, and smooth muscle are most markedly affected. Action of the inhibitors is overcome by increasing the level of acetylcholine naturally generated in the body through inhibiting the enzyme (cholinesterase) which normally prevents accumulation of excess acetylcholine. It does this by hydrolyzing that compound to inactive acetic acid and choline. Agents which inhibit this enzyme, so that acetylcholine accumulates at the neuroreceptor sites, are called anticholinesterases.

Physostigmine, one of the anticholine esterases which is a tertiary amine, crosses into the central nervous system and can reverse both central and peripheral anticholinergic actions.

The anticholinergic syndrome has both central and peripheral signs and symptoms. Central toxic effects include anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Severe poisoning may produce coma, medullary paralysis, and death. Peripheral toxicity is characterized by tachycardia, hyperpyrexia, mydriasis, vasodilatation, urinary retention, diminution of gastrointestinal motility, decrease of secretion in salivary and sweat glands, and loss of secretions in the pharynx, bronchi, and nasal passages.

Some drugs in the anticholinergic group, such as imipramine and related tricyclics also produce additional toxic effects such as cardiac arrhythmias which can be reversed by physostigmine.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Toxic effects from mixed drug ingestions and combination preparations such as amitriptyline and perphenazine may respond less dramatically. Since physostigmine is rapidly metabolized, therapeutic doses may be necessary at intervals as life-threatening signs such as arrhythmias, convulsions, and deep coma recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

CONTRAINDICATIONS: Physostigmine salicylate injections should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents (decamethonium, succinylcholine).

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions. An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur. Physostigmine salicylate is rapidly metabolized in the body.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED: Ampuls, 2 ml. packed 12 per box.

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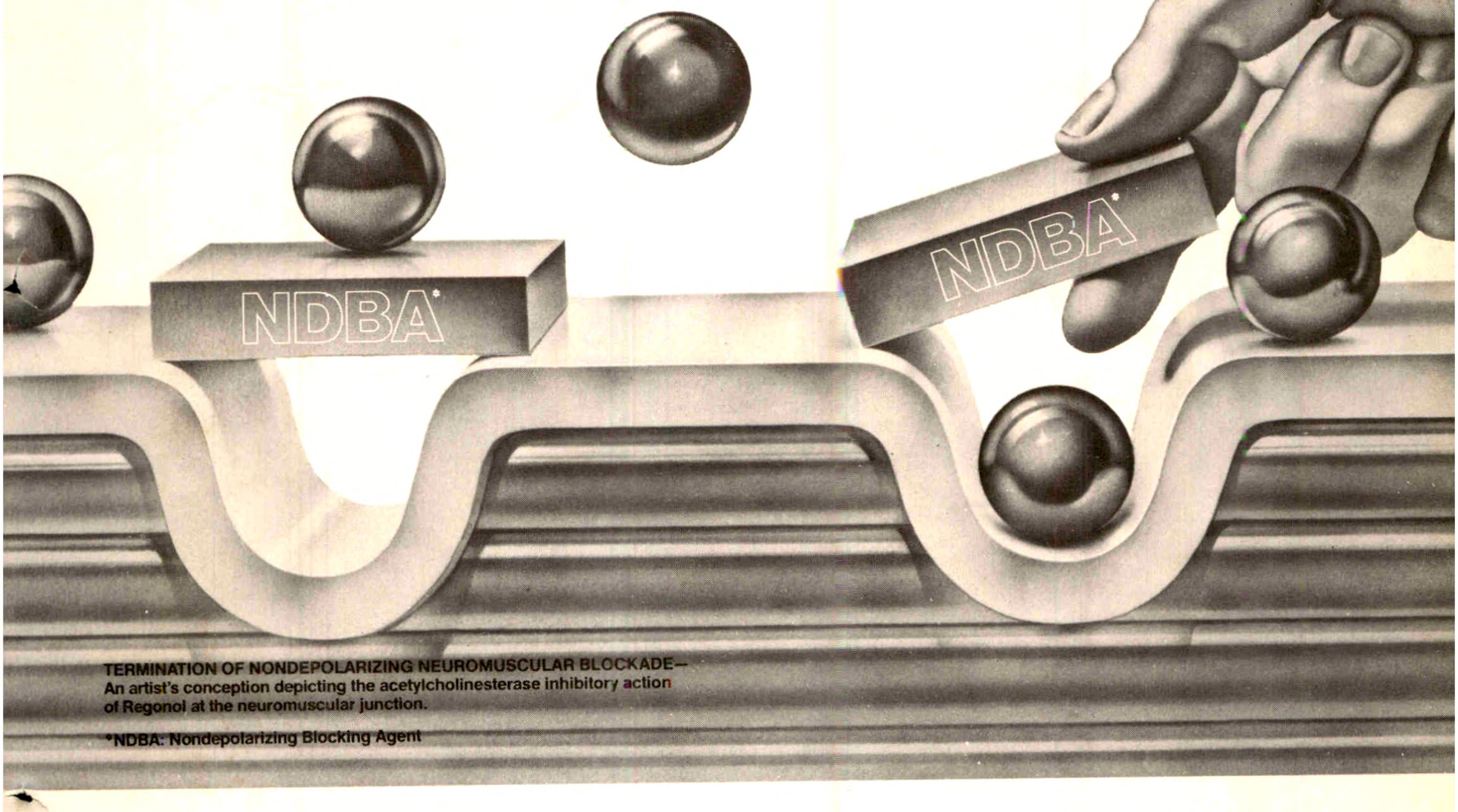

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Usage in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—Side effects are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—Prior or simultaneous administration of atropine sulfate (0.6 to 1.2 mg; I.V.) is recommended to minimize the side effects (excessive secretions, bradycardia). Usually 10 or 20 mg of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether.

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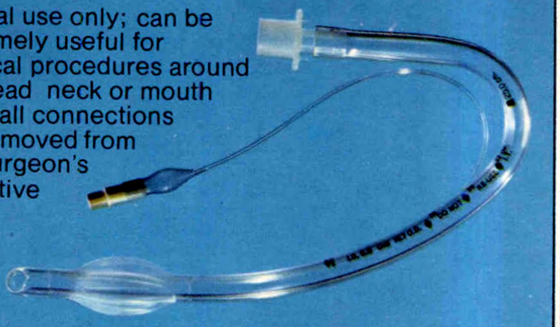

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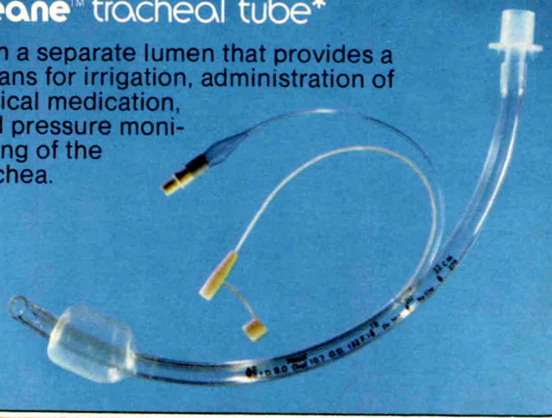

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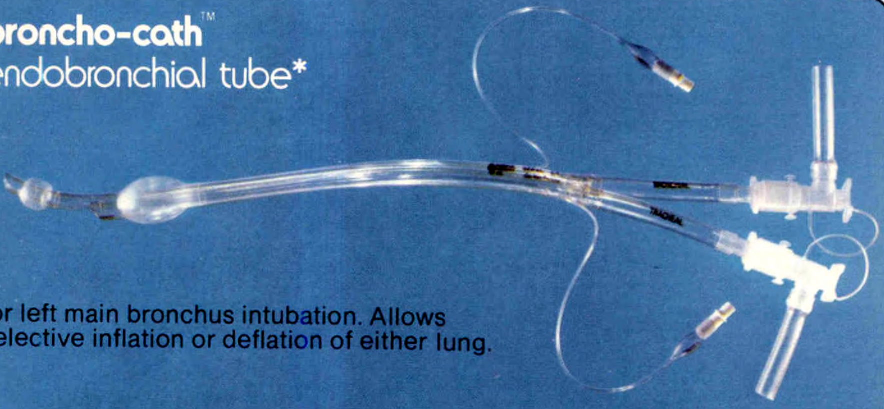

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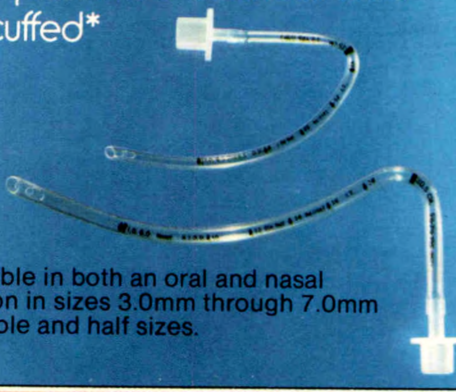

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Anesthesia and Analgesia

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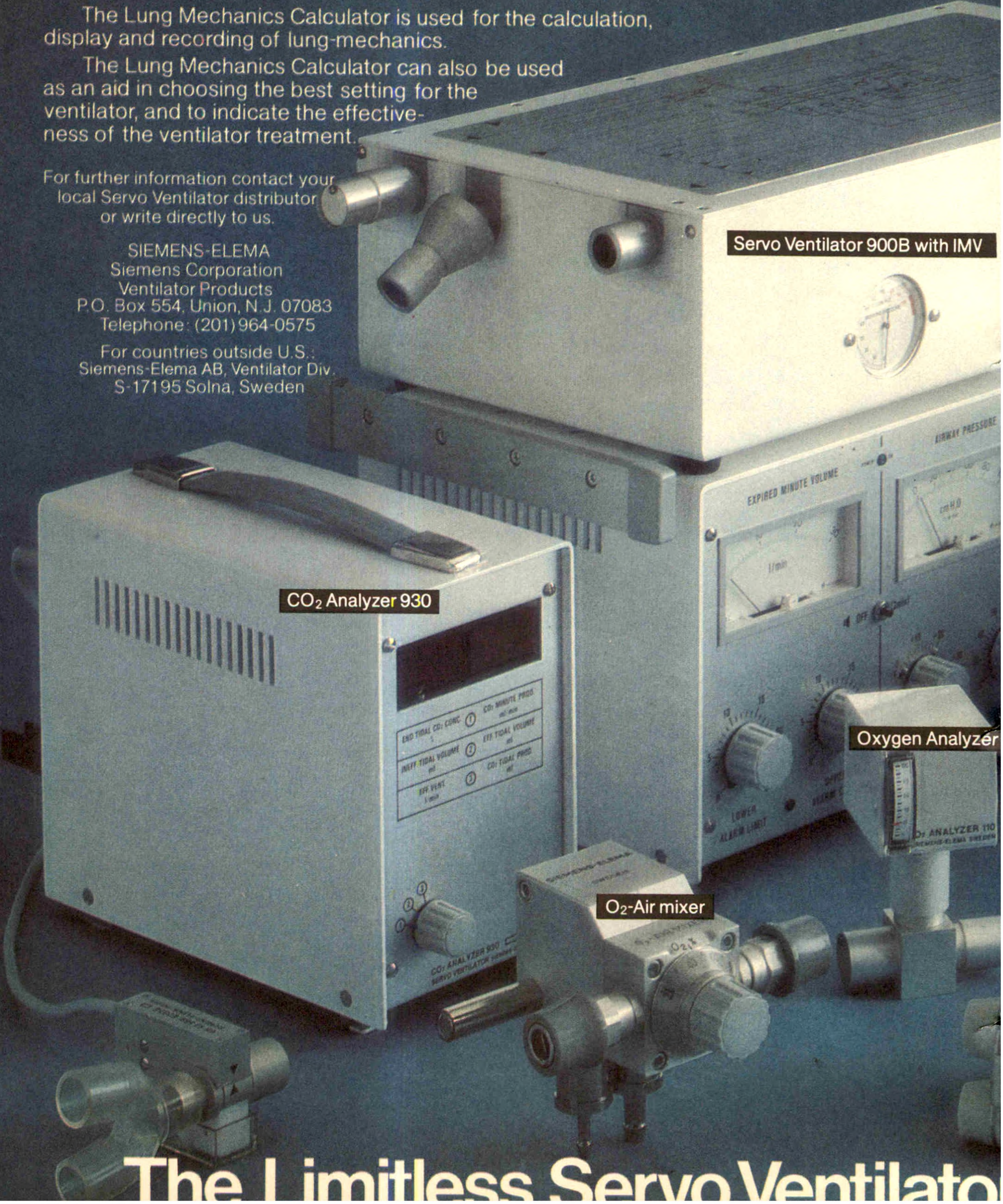

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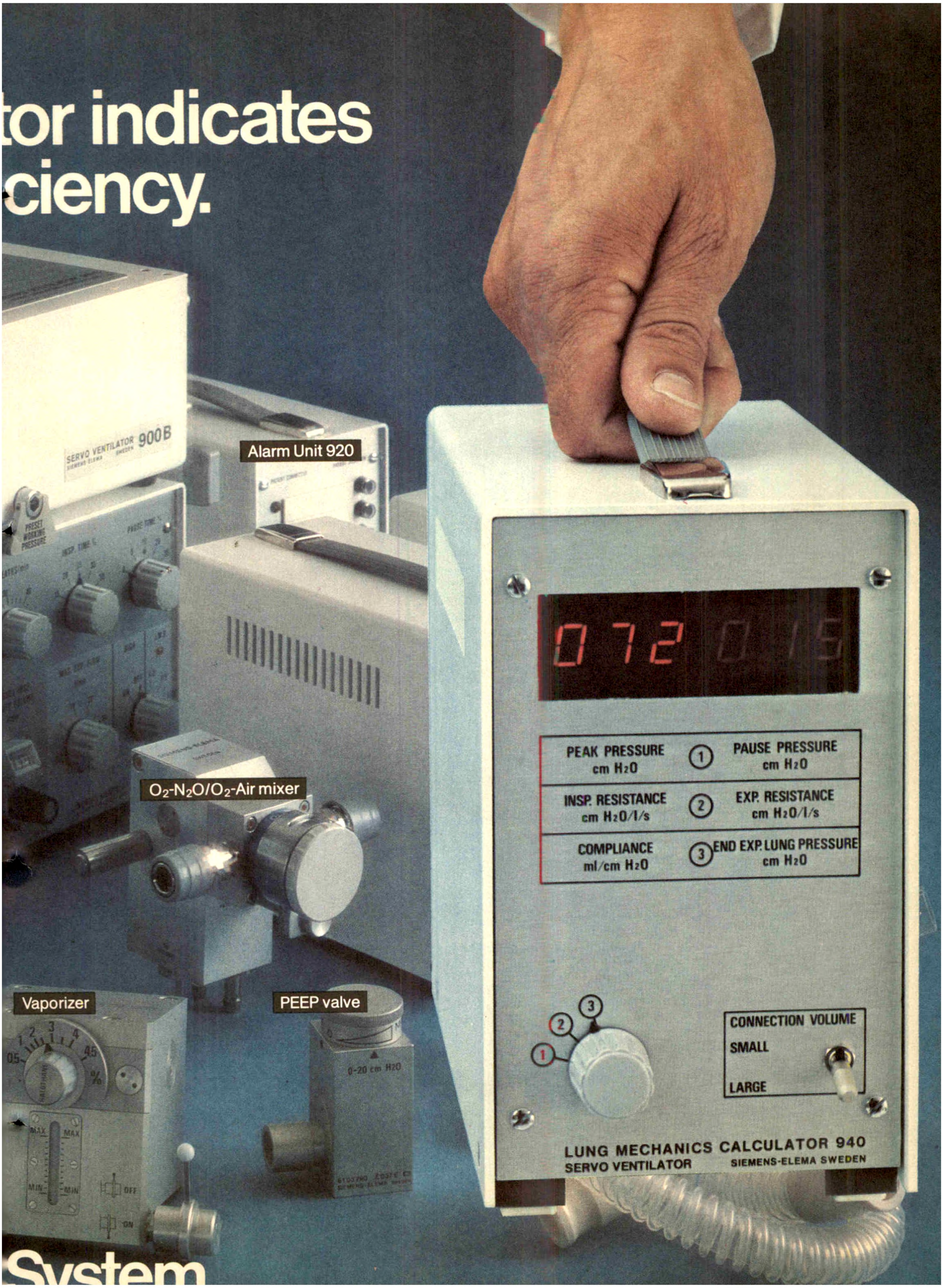

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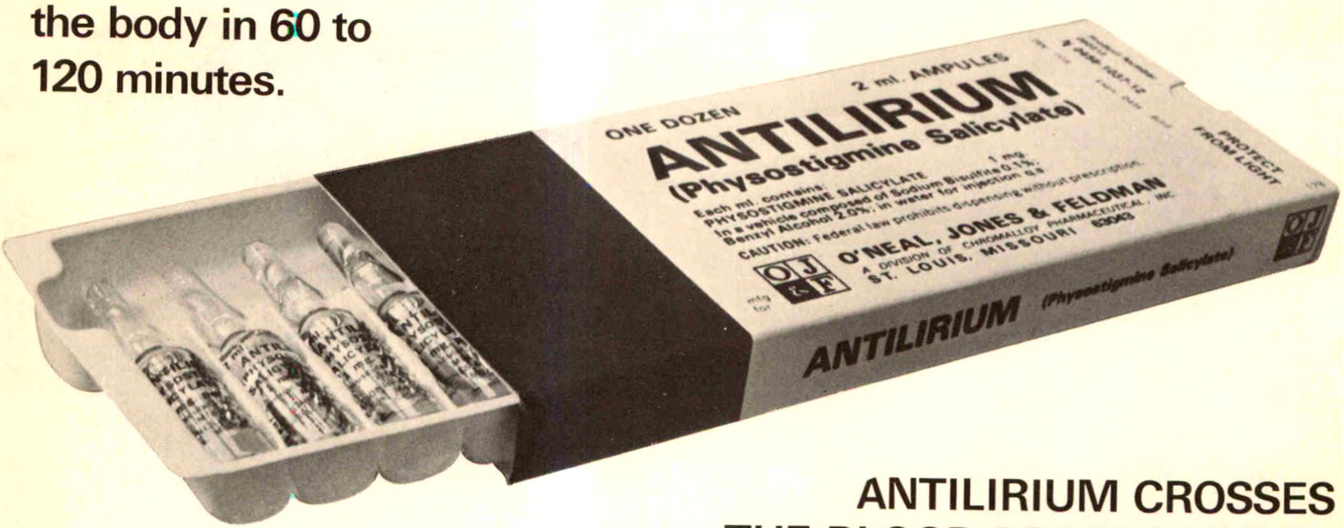
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ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. The action of acetylcholine is normally very fleeting because of its hydrolysis by a specific enzyme. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine. The changes in body function which are produced by the injection of physostigmine are, therefore, very similar to those which would occur from simultaneous stimulation of the parasympathetic nerves and include contraction of the pupil, increased tonus of the intestinal musculature, constriction of the bronchi and stimulation of secretion of the salivary and sweat glands.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quarternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Drugs with anticholinergic properties primarily antagonize acetylcholine competitively at the neuroreceptor site. Cardiac muscle, exocrine glands, and smooth muscle are most markedly affected. Action of the inhibitors is overcome by increasing the level of acetylcholine naturally generated in the body through inhibiting the enzyme (cholinesterase) which normally prevents accumulation of excess acetylcholine. It does this by hydrolyzing that compound to inactive acetic acid and choline. Agents which inhibit this enzyme, so that acetylcholine accumulates at the neuroreceptor sites, are called anticholinesterases.

Physostigmine, one of the anticholine esterases which is a tertiary amine, crosses into the central nervous system and can reverse both central and peripheral anticholinergic actions.

The anticholinergic syndrome has both central and peripheral signs and symptoms. Central toxic effects include anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Severe poisoning may produce coma, medullary paralysis, and death. Peripheral toxicity is characterized by tachycardia, hyperpyrexia, mydriasis, vasodilatation, urinary retention, diminution of gastrointestinal motility, decrease of secretion in salivary and sweat glands, and loss of secretions in the pharynx, bronchi, and nasal passages.

Some drugs in the anticholinergic group, such as imipramine and related tricyclics also produce additional toxic effects such as cardiac arrhythmias which can be reversed by physostigmine.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Toxic effects from mixed drug ingestions and combination preparations such as amitriptyline and perphenazine may respond less dramatically. Since physostigmine is rapidly metabolized, therapeutic doses may be necessary at intervals as life-threatening signs such as arrhythmias, convulsions, and deep coma recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

CONTRAINDICATIONS: Physostigmine salicylate injections should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents (decamethonium, succinylcholine).

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions. An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur. Physostigmine salicylate is rapidly metabolized in the body.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

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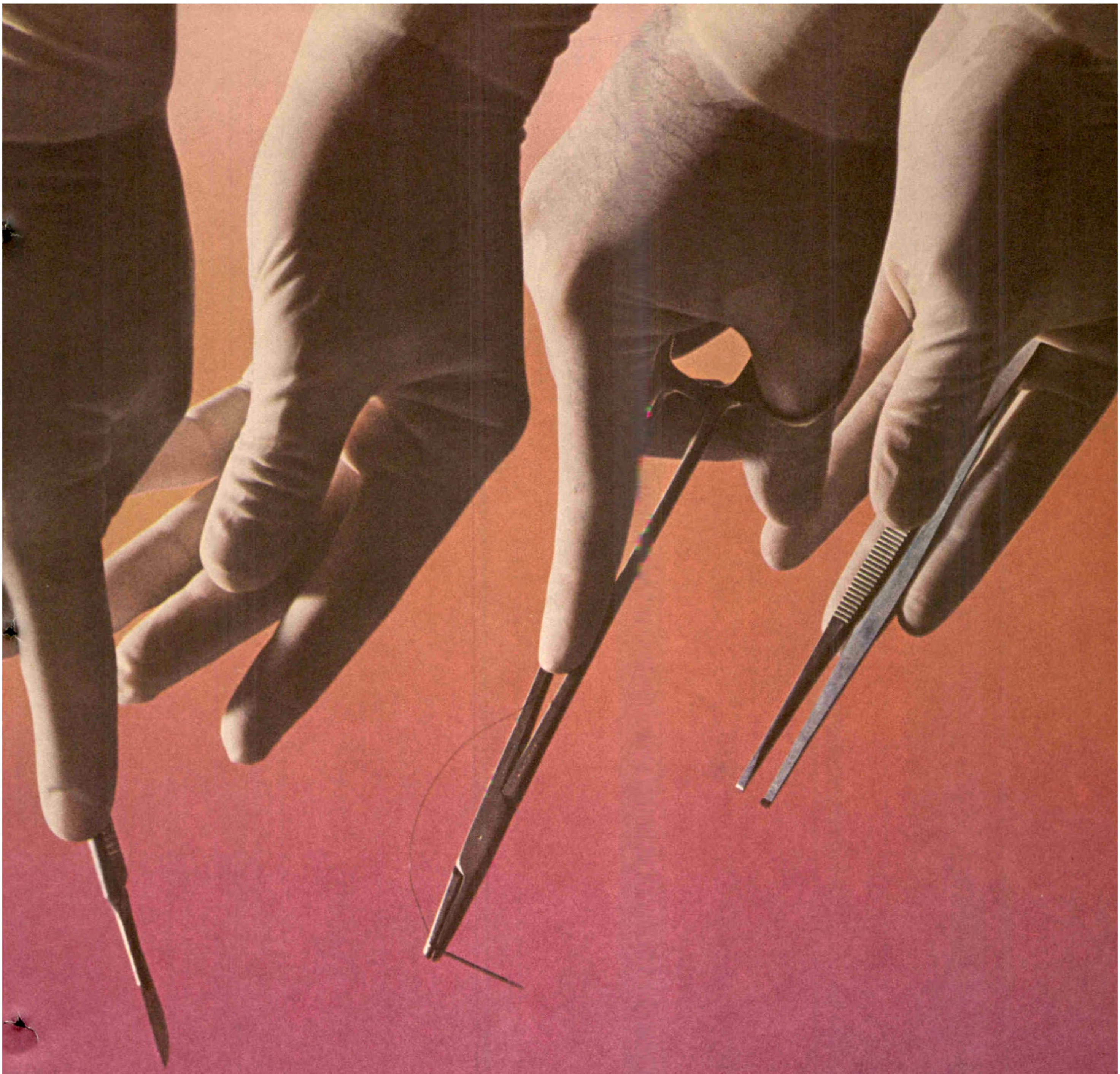

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Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

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Reference:
1. Stanley and Liu. Anesth Analg 56:669, 1977

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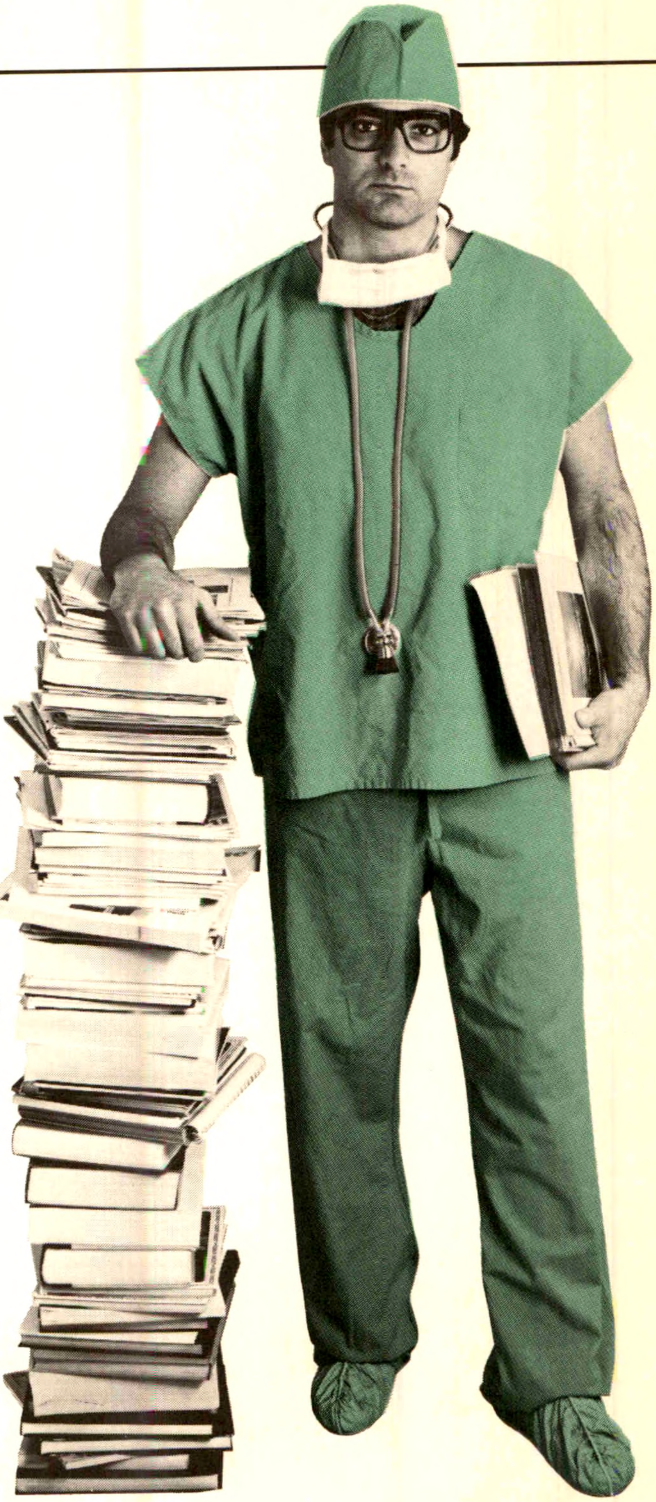

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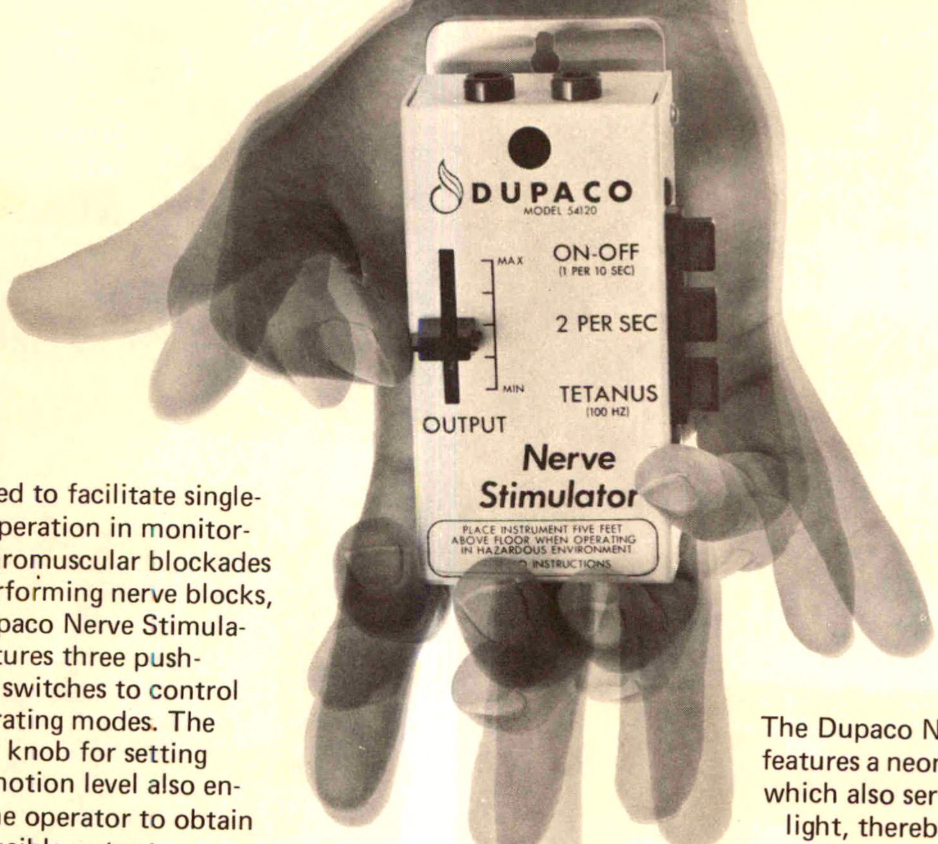

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- Protects against excessive volume and acidity of gastric secretions—a danger if pulmonary aspiration occurs.
- Protects against vagal reflexes at time of intubation.

INTRA- OR POST-OPERATIVELY

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- Protects against surgically-induced vagal reflexes.

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an anticholinergic with significant advantages over atropine

Situation	Objective	Action
preoperative	Reduction of gastric secretions plus elevation of gastric pH above 2.5 to help protect against serious sequelae of aspiration.	Use Robinul Injectable in the premedication regimen.
induction of anesthesia	To have unobstructed view of glottis prior to tracheal intubation. To help protect against vagal reflexes during intubation.	Use Robinul Injectable in the premedication regimen.
intra-operative	To help protect against surgically or drug induced vagal reflexes.	Use Robinul Injectable intraoperatively.
post-operative	To help prevent excess peripheral muscarinic effects of cholinergic agents used in the reversal regimen.	Use Robinul Injectable in the reversal regimen.
recovery room	To help prevent "central anticholinergic syndrome."	Use Robinul Injectable whenever an anticholinergic is used.

Each 1 ml contains:

Glycopyrrolate, NF	0.2 mg
Water for Injection, USP	q.s.
Chlorobutanol, USP (preservative)	0.5%

For intramuscular or intravenous administration in conjunction with anesthesia.

Contraindications: There are no absolute contraindications to the use of Robinul Injectable in conjunction with anesthesia except known hypersensitivity to glycopyrrolate.

Warnings: This drug should be used with great caution, if at all, in patients with glaucoma or asthma.

Precautions: *Usage in Pregnancy.* The use of any drug in pregnancy, lactation, or in the childbearing age requires that the potential benefits of the drug be weighed against the possible hazards to mother and child. Reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate. However, diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

Use with caution in patients with: myasthenia gravis; coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertension.

The intravenous administration of any anticholinergic in the presence of cyclopropane anesthesia can result in ventricular arrhythmias; therefore, caution should be observed if Robinul (glycopyrrolate) Injectable must be used during cyclopropane anesthesia. If the drug is given in small incremental doses of 0.1 mg or less, the likelihood of producing ventricular arrhythmias is reduced.

Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur.

Adverse Reactions: Anticholinergics produce certain effects most of which are extensions of their fundamental pharmacological actions. Adverse reactions to anticholinergics in general may include dry mouth; urinary hesitancy and retention; blurred vision due to mydriasis; increased ocular tension; tachycardia; palpitation; decreased sweating; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestation; some degree of mental confusion and/or excitement, especially in elderly persons.

Dosage and Administration: Robinul (glycopyrrolate) Injectable may be administered intramuscularly, or intravenously, without dilution, in the following indications:

Adults: *Preanesthetic Medication.* The recommended dose of Robinul (glycopyrrolate) Injectable is 0.002 mg (0.01 ml) per pound of body weight by intramuscular injection, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Robinul (glycopyrrolate) Injectable may be used during surgery to counteract drug-induced or vagal traction reflexes with the associated arrhythmias (e.g., bradycardia). It should be administered intravenously as single doses of 0.1 mg (0.5 ml) and repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Children: *Preanesthetic Medication.* The recommended dose of Robinul (glycopyrrolate) Injectable in children up to 12 years of age is 0.002 mg to 0.004 mg (0.01 ml to 0.02 ml) per pound of body weight intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Because of the long duration of action of Robinul (glycopyrrolate) if used as preanesthetic medication, additional Robinul (glycopyrrolate) Injectable for anticholinergic effect intraoperatively is rarely needed; in the event it is required the recommended pediatric dose is 0.002 mg (0.01 ml) per pound of body weight intravenously, not to exceed 0.1 mg (0.5 ml) in a single dose which may be repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended pediatric dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Compatibility With Other Agents: *Known compatibilities.* Robinul (glycopyrrolate) Injectable is compatible for mixing and injection with the following: 5% and 10% glucose in water or saline; Demerol® (meperidine) Injectable; morphine sulfate; Innovar® (fentanyl plus droperidol) Injectable; Vistaril® (hydroxyzine) Injectable; Prostigmin® (neostigmine) Injectable; Mestinon® (pyridostigmine) Injectable. Robinul Injectable may be administered via the tubing of a running infusion of physiological saline or lactated Ringer's solution.

Known incompatibilities include the following injectables: sodium bicarbonate; Valium® (diazepam); sodium pentobarbital; various phenothiazines; Dramamine® (dimenhydrinate), and chloramphenicol.

Drug Interaction During Anesthesia. Glycopyrrolate has been used clinically with at least the following medications: a barbiturate (sodium thiopental); narcotic analgesics (morphine, alphaprodine hydrochloride, fentanyl); sedative/tranquilizers (droperidol, diazepam); gaseous anesthetics (nitrous oxide); volatile liquid anesthetics (diethyl ether, halothane, methoxyflurane, enflurane); parenteral anesthetics (ketamine); peripherally-acting skeletal muscle relaxants (succinylcholine, gallamine, d-tubocurarine, pancuronium); cholinergic agents (neostigmine, pyridostigmine); and other anticholinergics (atropine).

There are no known unique or unanticipated drug-drug interactions with other agents except that Robinul (glycopyrrolate) Injectable should be used with caution if at all during cyclopropane anesthesia (see Precautions).

Management of Overdosage: To combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulfate may be given in a dose of 1.0 mg for each 1.0 mg of Robinul (glycopyrrolate) Injectable known to have been administered.

How Supplied: Robinul (glycopyrrolate) Injectable is available in 1 ml single dose vials; and 5 ml and 20 ml multiple dose vials (NDC 0031-7890).

Rev. Aug. 1976

A.H. Robins Company, Richmond, Va. 23220

A-H-ROBINS

for intramuscular or intravenous administration in conjunction with anesthesia

Robinul® Injectable

(Glycopyrrolate Injection, NF)

Ēthrane®

(enflurane

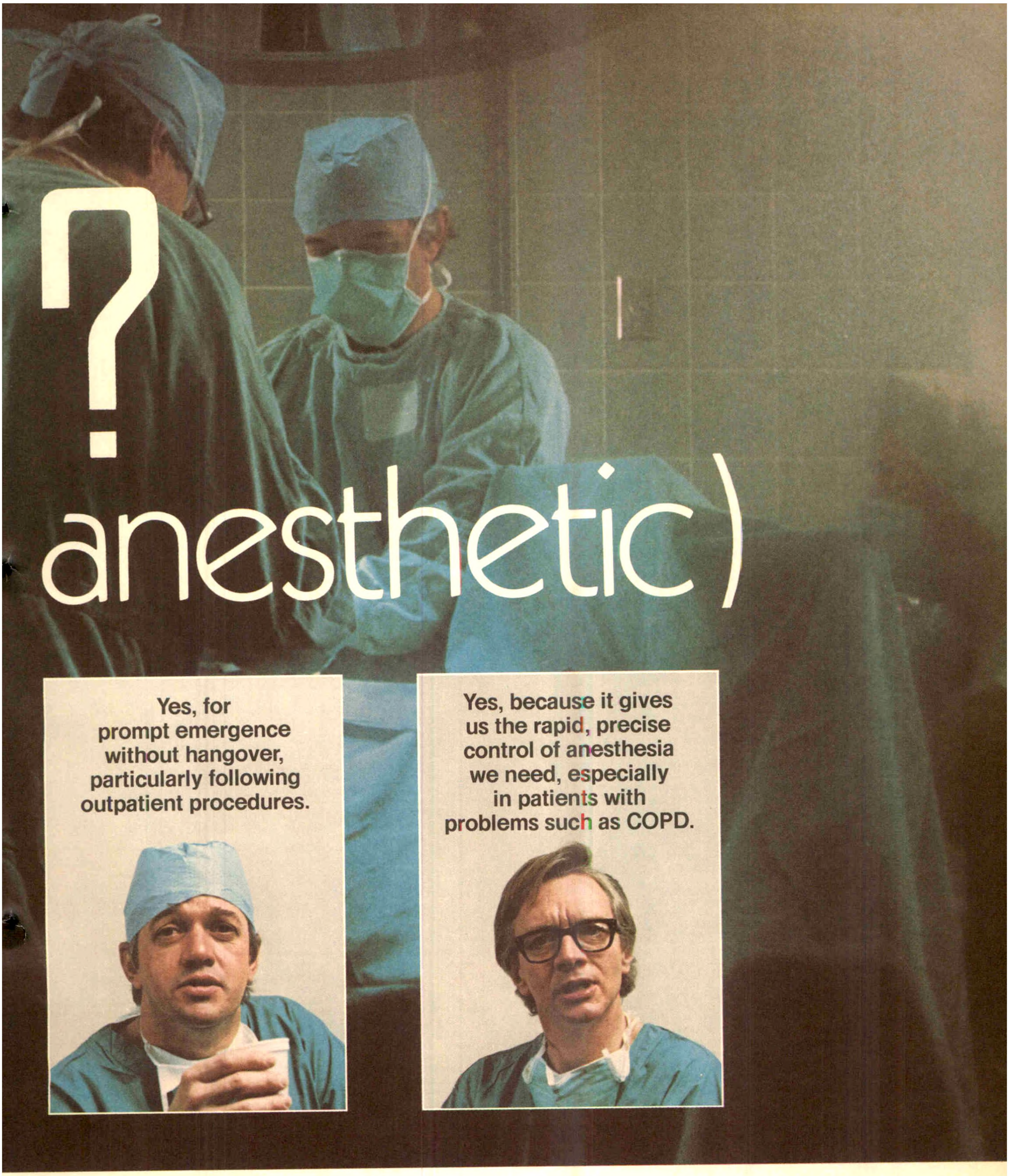
Yes, for its inherent muscle-relaxant effect in cholecystectomies and other abdominal surgeries.

Yes, because it allows more latitude in our use of epinephrine for hemostasis, particularly in head and neck surgeries.

ĒTHRANE (enflurane)—with its low solubility in blood, inherent muscle-relaxant effect, and apparent lack of cardiac arrhythmic effect—offers you and your surgeons more control and more flexibility. And for patient comfort it provides smooth, rapid inductions, prompt emergence (with no need for narcotic reversal agents), and an early sense of alertness and well-being.

Facts About ĒTHRANE (enflurane)

- Blood-gas partition coefficient—1.9 @ 37°C.
- Compatibility with epinephrine—up to three 10 ml. injections of epinephrine solution (1:100,000 or 1:200,000) may be given within an hour.
- Concomitant muscle-relaxant dosage—(if needed) only ½ to ⅓ the usual requirements of nondepolarizing agents.


?
anesthetic)
Yes, for prompt emergence without hangover, particularly following outpatient procedures.
Yes, because it gives us the rapid, precise control of anesthesia we need, especially in patients with problems such as COPD.

New ĒTHRANE (enflurane) Compendium and Reference

Virtually all of the known facts about this remarkably versatile anesthetic—along with succinctly phrased, informative clinical data—are now available to you and your staff in the new, updated *ĒTHRANE (enflurane) Compendium and Reference*. Ask your OHIO Anesthetic Agents Representative for your copy or write to us in Madison. For a summary of complete usage information, please see the following page.

Ohio Medical Products
3030 Airco Drive, Madison, Wisconsin 53707

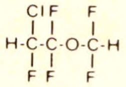
AIRCO®

Ēthrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ĒTHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$\begin{array}{ccccccccccc} & & \text{Cl} & & \text{F} & & & & \text{F} & & \\ & & | & & | & & & & | & & \\ \text{H} & - & \text{C} & - & \text{C} & - & \text{O} & - & \text{C} & - & \text{H} \\ & & | & & | & & & & | & & \\ & & \text{F} & & \text{F} & & & & \text{F} & & \end{array}$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \qquad A = 7.967$$
$$B = -1678.4$$
$$T = {}^\circ C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ĒTHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ĒTHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ĒTHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

ACTIONS

ĒTHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ĒTHRANE are rapid. ĒTHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ĒTHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ĒTHRANE. ĒTHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ĒTHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ĒTHRANE anesthesia. ĒTHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ĒTHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ĒTHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ĒTHRANE.

Biotransformation of ĒTHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ĒTHRANE anesthesia in man in the absence of surgery. Thus ĒTHRANE does not depress this aspect of the immune response.

INDICATIONS

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ĒTHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ĒTHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ĒTHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ĒTHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ĒTHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ĒTHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ĒTHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ĒTHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ĒTHRANE mixture. In general, inspired concentrations of 3.5-4.5% ĒTHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ĒTHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ĒTHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

PACKAGING

ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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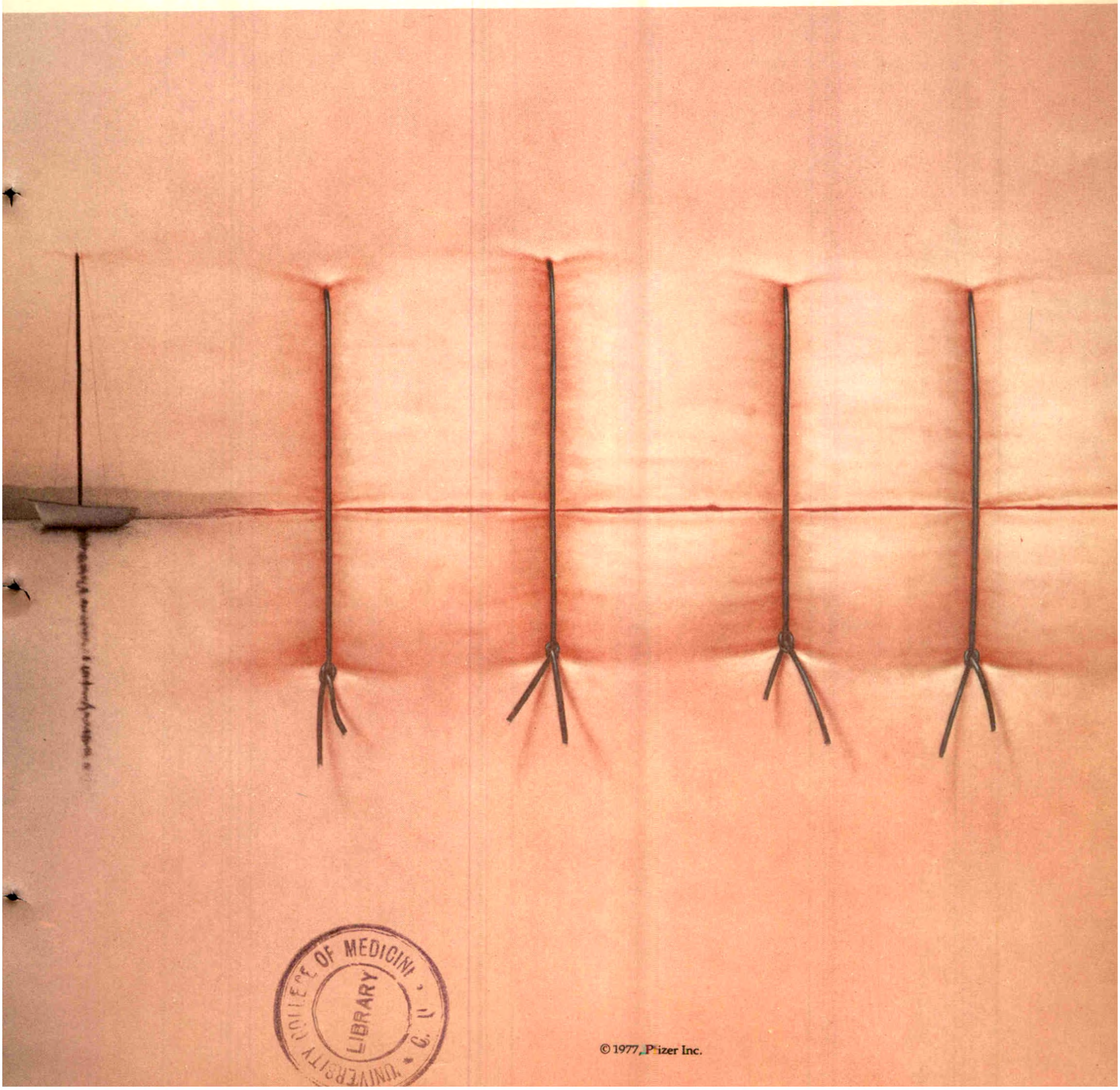
The Calm introduction to surgery

Vistaril® I.M.
(hydroxyzine HCl)

—allays anxiety
—reduces narcotic requirements
—and controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety...allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY
VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only
Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.
Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.
Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.
Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.
Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.
Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)
VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)
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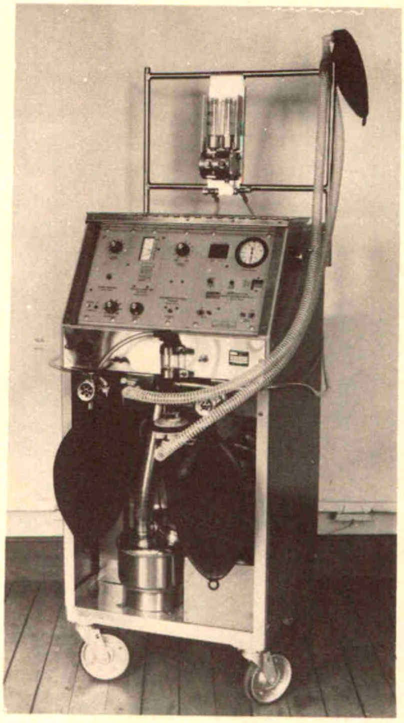

Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

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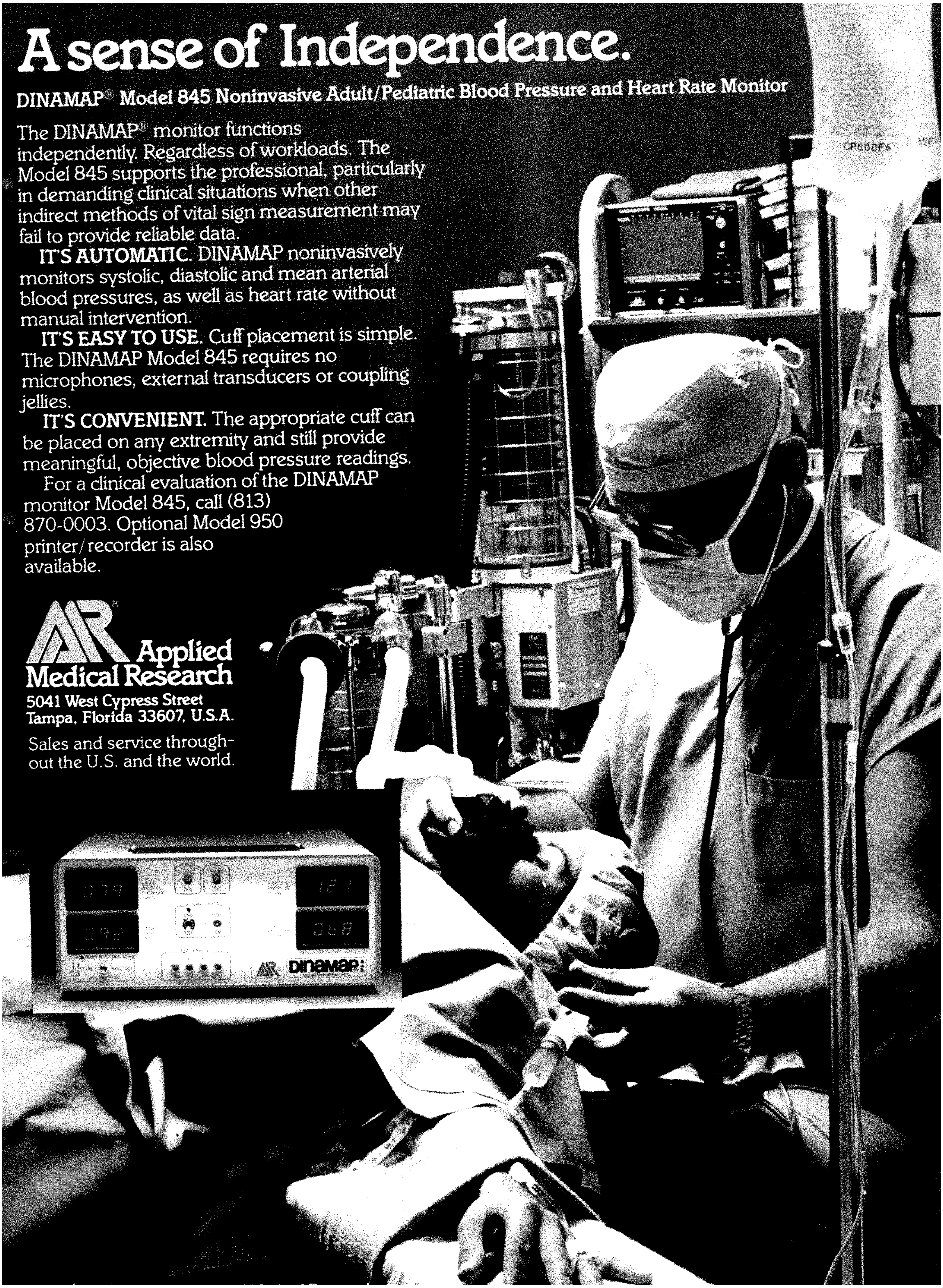

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The DINAMAP® monitor functions independently. Regardless of workloads. The Model 845 supports the professional, particularly in demanding clinical situations when other indirect methods of vital sign measurement may fail to provide reliable data.

IT'S AUTOMATIC. DINAMAP noninvasively monitors systolic, diastolic and mean arterial blood pressures, as well as heart rate without manual intervention.

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TITRATES THE RESPIRATORY DEPRESSION OUT

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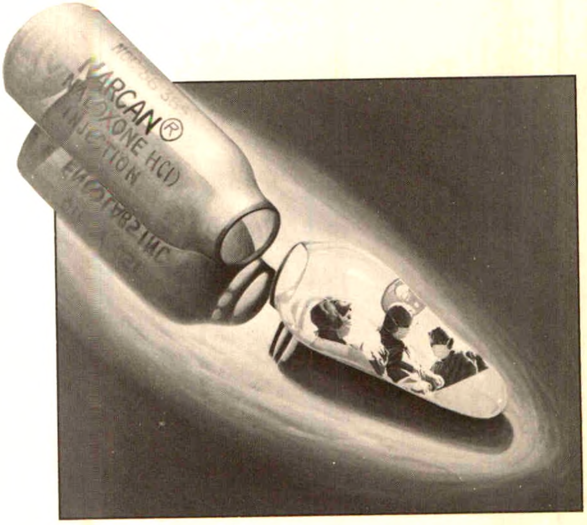

NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

Useful when narcotic/N_2O anesthesia is employed

Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism

The duration of activity of some narcotics may exceed that of NARCAN®. Observe the patient closely and give repeat doses of NARCAN® if needed.

Also available, NARCAN® NEONATAL naloxone HCl

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NARCAN®
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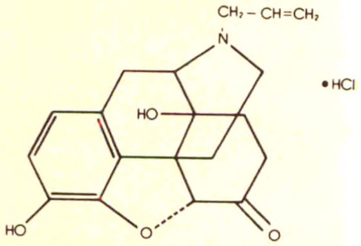
DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

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Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

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May, 1977

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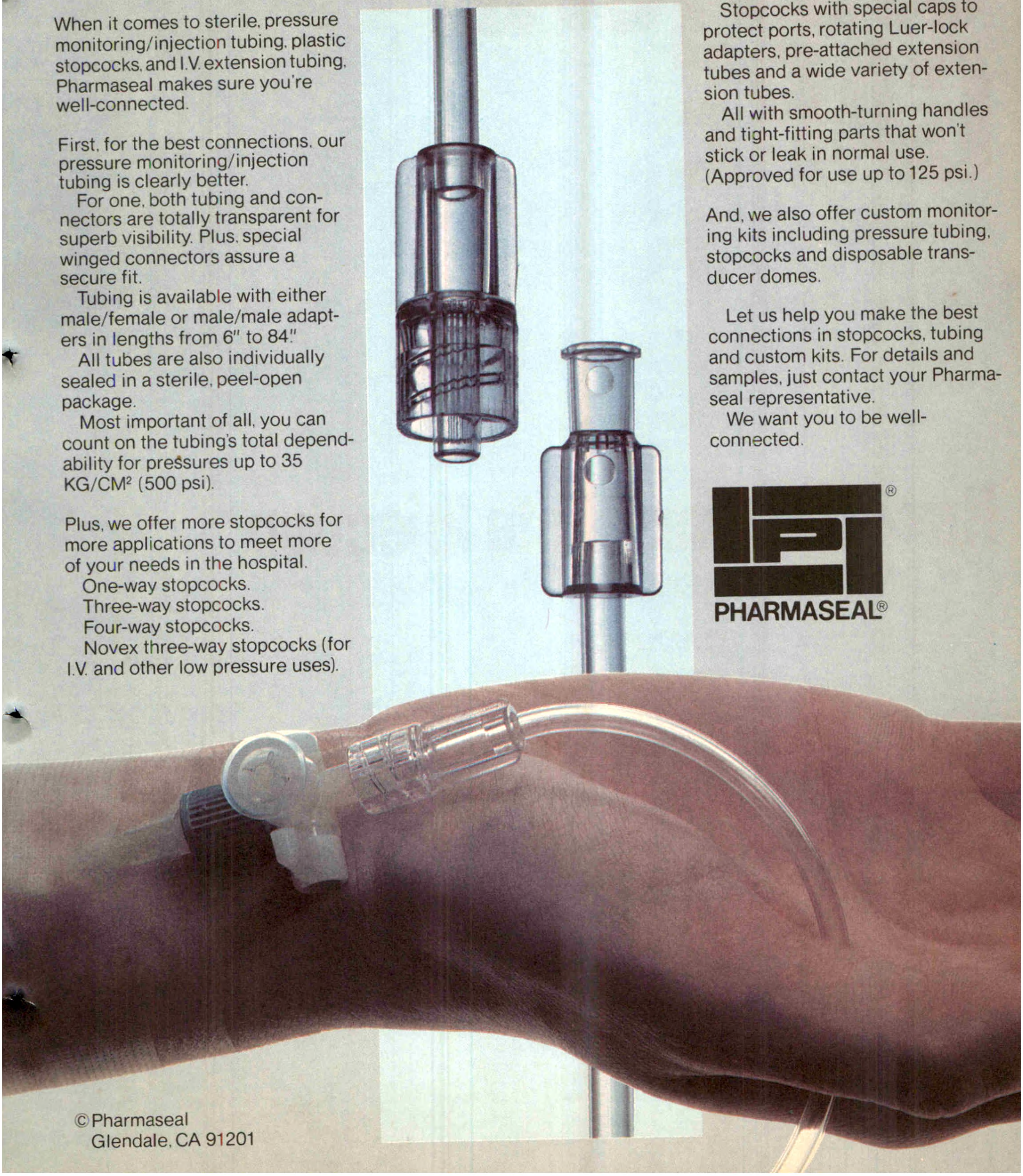

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Hexadrol® phosphate injection is easy to handle, store and administer. Already in solution, it can be used directly from the vial. Hexadrol has benzyl alcohol as a preservative and is stable at room temperature.

The multi-dose vial minimizes waste. When used in pharmacologic doses, Hexadrol offers significant savings over methylprednisolone.*

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BEFORE PRESCRIBING OR ADMINISTERING, PLEASE CONSULT COMPLETE PRODUCT INFORMATION, A SUMMARY OF WHICH FOLLOWS:

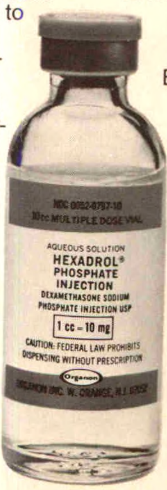
ACTIONS—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

CONTRAINDICATIONS—Systemic fungal infections—Hypersensitivity to any component.

WARNINGS—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage In Pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary salt restriction and potassium supplementation may be necessary.



100 mg

All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

PRECAUTIONS—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex for fear of corneal

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, approrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

ADVERSE REACTIONS—

Fluid and electrolyte disturbances: Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

Musculoskeletal: Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

Dermatologic: Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

Neurological: Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; Increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Miscellaneous: Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

DOSAGE AND ADMINISTRATION—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.

CAUTION—Federal law prohibits dispensing without prescription.

HOW SUPPLIED—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25; 10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

Hexadrol is available in two potencies, 4mg/cc and 10mg/cc in aqueous solution with 1% benzyl alcohol as preservative.

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This information will be mailed in December to all I.A.R.S. members, associate members, and educational members.

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EDITORIAL

Blood Levels of Local Anesthetics during Spinal and Epidural Anesthesia

PHYSIOLOGIC responses to spinal anesthesia have for many years been ascribed solely to block of nerve conduction within the subarachnoid space.[1] Particular importance has been attached to the consequences of interruption of nerve impulse transmission within preganglionic sympathetic fibers. Indeed, cardiovascular responses to spinal anesthesia have been said to represent the physiology of sympathetic denervation. Subarachnoid block of somatic motor fibers and at least partial block of superficial tracts within the spinal cord also occur but generally are regarded as being substantially less important. Block of somatic sensory fibers, although the *raison d'etre* of spinal anesthesia, is also devoid of significant physiologic effects. Blood levels of local anesthetics during spinal anesthesia have been assumed to be so low as to be unassociated with any significant pharmacologic effects on either the cardiovascular system or any other system. The amounts of local anesthetic injected into the subarachnoid space during spinal anesthesia have been felt to be too modest and their rates of absorption into the vascular system too slow to produce plasma concentrations of local anesthetics adequate to elicit systemic responses. In the absence of measurements of plasma levels of local anesthetics during spinal anesthesia, this concept has been based on theory, not hard data.

Physiologic responses to epidural anesthesia, on the other hand, have been explained on the basis of a combination of two factors: sympathetic denervation analogous to that observed during spinal anesthesia, plus plasma levels of local anesthetics (and vasoconstrictors, when used) great enough to exert direct pharmacologic effects on peripheral smooth muscle and the myocardium.[2,3] The fact that equal sensory levels of spinal and epidural anesthesia are associated with quite different cardiovascular responses has been said to be due mainly to differences in plasma levels of local anesthetics (and vasoconstrictors) associated with the two techniques. Equal sensory levels of anesthesia are, of course, accompanied by less extensive sympathetic blockade during epidural anaesthesia than during spinal anesthesia because the zone of differential blockade during spinal anesthesia is absent during epidural anesthesia. This, however, is probably less important in explaining the differences in cardiovascular function during the two types of anesthesia.

Classic concepts of the etiology of the cardiovascular responses to spinal anesthesia require reevaluation in view of the data reported by Giasi, D'Agostino, and Covino in the present issue of this journal.[4] For the first time data are reported on plasma levels of a local anesthetic during spinal anesthesia. That blood levels of local anesthetics have never before been reported with a regional anesthetic technique that has enjoyed such popularity for three-quarters of a century is remarkable in itself. Even more remarkable is their finding that peak plasma levels of lidocaine following injection of lidocaine into the lumbar epidural space are no different than they are when an equal amount of lidocaine is injected into the lumbar subarachnoid space. Blood levels are achieved more rapidly with epidural than with spinal anesthesia, to be sure, and this is, no doubt, due to differences in vascularity and rates of absorption, as the authors suggest. But there is no statistically significant difference in the maximum plasma concentrations.

What are we to make of this important observation? Does it mean, for example, that cardiovascular responses to spinal anesthesia can no longer be ascribed simply and solely to sympathetic denervation? Should we now regard the physiologic effects of spinal anesthesia as being due to a combination of both sympathetic block and pharmacologically active concentrations of local anesthetic, as with epidural anesthesia? Perhaps, but this appears unlikely, at least on the basis of the information presently available. For one thing, in the patients studied by Giasi et al, there was no relation between plasma levels of lidocaine and changes in blood pressure during spinal anesthesia. Systolic blood pressure decreased slightly but significantly 2 minutes after the subarachnoid injection of lidocaine. In three patients hypotension was severe enough to require treatment with ephedrine. Yet at the time hypotension was present plasma lidocaine levels averaged about 0.025 μg/ml (figure 1 in Giasi et al). On the other hand, by the time average plasma levels of lidocaine had reached peak concentrations of 0.32 μg/ml (15 minutes after induction of spinal anesthesia) the blood pressure had returned to preanesthetic control levels. Thus, it still appears that the initial changes in blood pressure during spinal anesthesia are primarily related not to blood levels of lidocaine but to rapid onset of sympathetic block. Why blood pressure returned to normal levels despite the presence of peak plasma levels of lidocaine, even though blood pressure was significantly decreased 2 minutes after induction of anesthesia, can be explained on the basis of one or both of two reasons. First, blood levels of 0.32 μg/ml of lidocaine exert no significant effect on blood pressure. Second, reflex mechanisms set in motion by the initial hypotension and sympathetic denervation, including vasoconstriction in sympathetically intact portions of the body, compensate within 15 minutes for early hypotensive responses to spinal anesthesia. In the study of Giasi et al, an additional factor may have been that three of the 10 patients who had spinal anesthesia received 25 mg of ephedrine intravenously. This may have skewed mean arterial blood pressure levels at 15 minutes, when data obtained in all 10 patients were pooled.

Equally necessary in the clinical interpretation of these important data of Giasi and associates is recognition of the fact that equal levels of surgical (or obstetrical) anesthesia are not obtained when equal amounts of local anesthetic are injected into the lumbar epidural or subarachnoid spaces. The authors give no data on the levels of sensory anesthesia obtained in their patients, but it would appear improbable that 75 mg (3.75 ml of a 2% solution) of lidocaine injected into the lumbar epidural space would produce sensory levels of anesthesia as extensive as those usually obtained by injection of 75 mg (1.5 ml of a 5% solution) of lidocaine into the lumbar subarachnoid space. By the same token, the amount of lidocaine needed to achieve surgical anesthesia to, say, the level of the sixth thoracic dermatome is significantly greater during epidural anesthesia than it is during spinal anesthesia. As the authors point out, plasma levels of local anesthetics are determined, *inter alia*, by dosage. Plasma concentrations would thus be expected to be greater during epidural anesthesia than during equal sensory levels of spinal anesthesia. Plasma lidocaine levels during epidural anesthesia under these conditions may well be great enough to produce peripheral cardiovascular effects even though plasma lidocaine levels during equal sensory levels of spinal anesthesia remain inadequate to achieve pharmacologically effective concentrations in the systemic circulation. Cardiovascular responses to epidural anesthesia could, thus, still be the result of a combination of sympathetic denervation plus systemic drug effect. Cardiovascular responses to spinal anesthesia could remain, as originally hypothesized, primarily the result of sympathetic block despite the fact that spinal anesthesia is accompanied by detectable plasma levels of local anesthetic.

The data reported by Giasi and associates make a major contribution to our understanding of the physiologic responses to these major regional anesthetic techniques. Further information is needed, however, before these data can be put into their proper clinical perspective. What are the plasma levels of more potent local anesthetics, e.g. tetracaine, during spinal anesthesia? Can plasma levels of a drug such as tetracaine be related to the cardiovascular perturbations associated with tetracaine spinal anesthesia? What are the dose-response curves for local anesthetics insofar as cardiovascular function and plasma levels are concerned? What are their plasma ED_{50}s . . . their plasma ED_{100}s? What is the effect on plasma levels of local anesthetics during spinal anesthesia when epinephrine is injected with the local anesthetic? Why does the plasma level of lidocaine appear to decrease more rapidly (i.e. have a shorter plasma half-life) after spinal anesthesia than after epidural anesthesia (figure 1 in Giasi et al)? If true allergy to local anesthetics exists on the basis of an antigen-antibody response, can we expect systemic "allergic" reactions to local anesthetics employed during spinal anesthesia? If so, why are they so rare as to be unreported?

Until such questions are answered, hopefully in the near future, we should bear in mind two things. First, lidocaine spinal anesthesia is associated with detectable plasma levels of lidocaine, the pharmacologic significance of which remains uncertain. And, second, although equal doses of lidocaine result in the same plasma levels of lidocaine when injected into the epidural or subarachnoid spaces, equal levels of sensory anesthesia are not produced by injection of equal doses of local anesthetic. Therefore, equal sensory levels of anesthesia are probably not associated with equal blood levels of local anesthetics when epidural and spinal anesthesia are compared. The fact that during epidural anesthesia blood levels of local anesthetics are achieved which are adequate to produce direct systemic effects on cardiovascular function does not mean that we can assume that during equal levels of spinal anesthesia blood levels of local anesthetics are also adequate to produce significant peripheral effects.

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Nicholas M. Greene, MD

Intravenous versus Endotracheal Epinephrine

Blood levels of epinephrine and its metabolites were obtained after the drug was given by both the intravenous (IV) and endotracheal (ET) routes in anesthetized dogs in doses of 0.005, 0.03, 0.06, and 0.09 mg/kg. Blood levels were obtained at 0.25, 0.75, 1.5, 3, 5, 10, and 30 minutes following injection. The maximum measured concentration following IV injection occurred at 15 seconds. Epinephrine was rapidly metabolized with 20% of the original concentration detected at 5 minutes following IV injection. After ET administration, the maximum measured concentration was present at 5 minutes. Maximum concentrations were approximately one tenth of those achieved with equal IV dosage. It is concluded that endotracheally and intravenously administered epinephrine rapidly reach maximum blood levels but there are differences in kinetics between the two routes. (*Roberts JR, Greenberg MI, Knaub MA, et al: Blood levels following intravenous and endotracheal epinephrine administration. JACEP 8:53–56, 1979*)

ANESTH ANALG
58:360-363, 1979

Absorption of Lidocaine following Subarachnoid and Epidural Administration

Robert M. Giasi, MD,* Eduardo D'Agostino, MD,† and Benjamin G. Covino, MD, PhD‡

GIASI, R. M., D'AGOSTINO, E., AND COVINO, B. G.: Absorption of lidocaine following subarachnoid and epidural administration. Anesth Analg 58:360–363, 1979.

The absorption of lidccaine into the vascular system from the epidural and subarachnoid spaces was determined in 20 patients. Seventy-five milligrams (1.5 ml of a 5% solution) of lidocaine was administered intrathecally to 10 patients for spinal anesthesia and 75 mg (3.75 ml of a 2% solution) was injected epidurally. Venous plasma levels of lidocaine were determined at 2, 5, 10, 15, and 30 minutes after subarachnoid or epidural injection. No significant differences existed between the maximum venous plasma concentrations of lidocaine following epidural injection (0.41 ± 0.07 μg/ml) and following subarachnoid injection (0.32 ± 0.07 μg/ml). However, the rate of vascular absorption of lidocaine from the subarachnoid space was significantly slower than from the epidural space. By 2, 5, and 10 minutes after injection, venous plasma concentrations of lidocaine were significantly higher following epidural injection than they were after subarachnoid injection. This variation was not attributable to differences in blood pressure following injection. The differential rate of absorption is probably related to the anatomical arrangement of the venous plexuses in the epidural and subarachnoid spaces.

Key Words: ANESTHETIC TECHNIQUES: spinal; ANESTHETIC TECHNIQUES: peridural; ANESTHETICS, Local: lidocaine.

THE SYSTEMIC absorption of local anesthetic agents is related primarily to the site of injection, dosage, and relative vasodilator properties of the individual local anesthetic drug and the presence or absence of a vasoconstrictor in the anesthetic solution. Previous studies[1-7] have demonstrated a similar pattern of absorption of lidocaine, prilocaine, mepivacaine, bupivacaine, and etidocaine from various sites of administration. The highest blood levels are obtained after intercostal nerve block;[1, 4, 5] followed, in order, by caudal, lumbar epidural, brachial plexus, sciatic femoral,[1-5] and subcutaneous administration.[3, 4] The high blood levels seen with intercostal nerve block result from the multiple injections required which expose the local anesthetic agent to a large vascular surface area. The bony matrix in the caudal canal is highly vascular accounting for the high blood levels seen with this injection site.[8] The adipose tissue in the lumbar epidural space serves as a depot for anesthetics resulting in lower blood levels.[1, 2, 6] Uptake of local anesthetic agents by subcutaneous adipose tissue may also account for the slow rate of vascular absorption observed following subcutaneous infiltration anesthesia.[4, 9]

Although spinal anesthesia represents one of the oldest forms of regional anesthesia, the rate of absorption of local anesthetic agents from the subarachnoid space has not been determined. A rapid decline in the spinal fluid concentration of local anesthetics

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has been observed following subarachnoid administration.[10, 11] This has been attributed to spreading of the anesthetic agent away from the site of injection, uptake by nerve tissue, and vascular absorption. Although, controlled comparative studies of spinal and epidural anesthesia are lacking, available clinical data suggest that the duration of spinal anesthesia is shorter than that of epidural analgesia which may be indicative of a more rapid rate of absorption of the local anesthetic agent from the subarachnoid space.[6] The present study was initiated to determine the relative rate of absorption of lidocaine from the epidural and subarachnoid space by the sequential determination of lidocaine blood levels.

Materials and Methods

Blood levels of lidocaine were determined in 20 patients following spinal or lumbar epidural administration of 75 mg of lidocaine. Dural puncture with a 25-gauge spinal needle was performed at $L_{2\text{-}3}$ in 10 patients in the lateral position. A volume of 1.5 ml of a hyperbaric 5% lidocaine solution (75 mg) was injected into the subarachnoid space. In 10 additional patients 75 mg of lidocaine (3.75 ml of a 2% solution) was injected extradurally via a catheter following identification of the epidural space by the loss of resistance technique at $L_{2\text{-}3}$. This served as the test dose prior to initiation of epidural anesthesia.

Patients having epidural anesthesia consisted of nine men and one woman with an average age of 44 ± 6.5 years. Five men and five women with an average age of 54 ± 6.4 years had spinal anesthesia. All patients received similar preoperative medication consisting of either meperidine, hydroxyzine with atropine or morphine, or diazepam with atropine intramuscularly 45 minutes before control blood samples were drawn. Only patients classified as A.S.A. physical status I or II were included in the study.

Venous blood samples were drawn from a catheter in the antecubital vein before and 2, 5, 10, 15, and 30 minutes after injection of 75 mg of lidocaine into either the epidural or subarachnoid space. Lidocaine concentrations in venous plasma were determined by means of gas chromatography.[12] Heart rate and blood pressure measured by standard sphygmomenometry were recorded at each sampling time. Statistical analysis was performed utilizing analysis of variance and Student's t-test. All values are expressed as means ± standard error.

Results

Fig 1 compares the mean venous plasma levels of lidocaine determined in both groups. There was no statistically significant difference in the maximum plasma concentrations of lidocaine following epidural (0.41 ± 0.07 μg/ml) and spinal (0.32 ± 0.7 μg/ml) anesthesia ($p > 0.1$). Peak plasma levels were achieved at 15 minutes in most subjects regardless of the site of injection. However, patients given epidural injections showed significantly higher levels of lidocaine at 2, 5, and 10 minutes as compared to the patients given spinal anesthesia ($p < 0.01$ or 0.05). No significant differences in mean heart rate, or systolic or diastolic blood pressures existed between the two groups during the 30-minute period following lidocaine administration (Fig 2). A small but significant decrease ($p < 0.01$) in systolic pressure was observed at 2 minutes (103 ± 5.7 mm Hg) following spinal anesthesia in comparison with the control value (112 ± 5.9 mm Hg). This was attributable to three patients in whom systolic pressure decreased 20 to 30 mm Hg following subarachnoid administration of lidocaine. Ephedrine (25 mg) was administered intravenously in these patients. No significant difference was observed between the control systolic and diastolic pressure and the systemic pressure 5 minutes after the subarachnoid administration of lidocaine. Since no significant difference in lidocaine plasma concentration existed between the three patients receiving ephedrine and the remaining seven patients, the data were

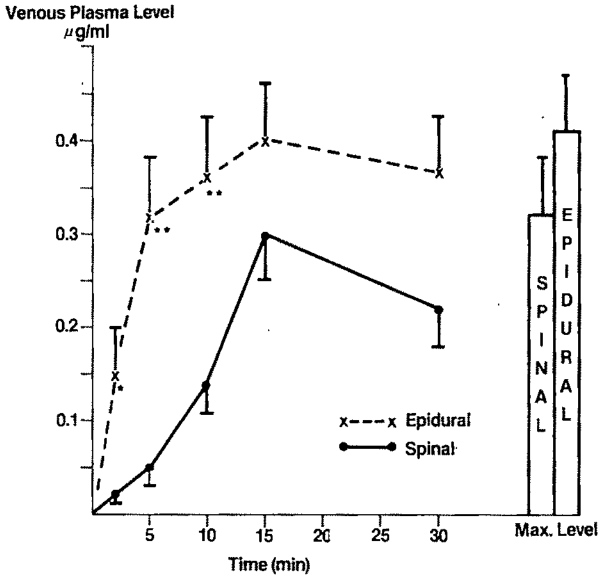

FIG 1. Mean ± SE venous plasma levels of lidocaine following epidural (upper curve) and subarachnoid (lower curve) administration. Bar graph shows mean ± SE maximum venous plasma levels of lidocaine following epidural or subarachnoid administration. * $p < 0.05$; ** $p < 0.01$.

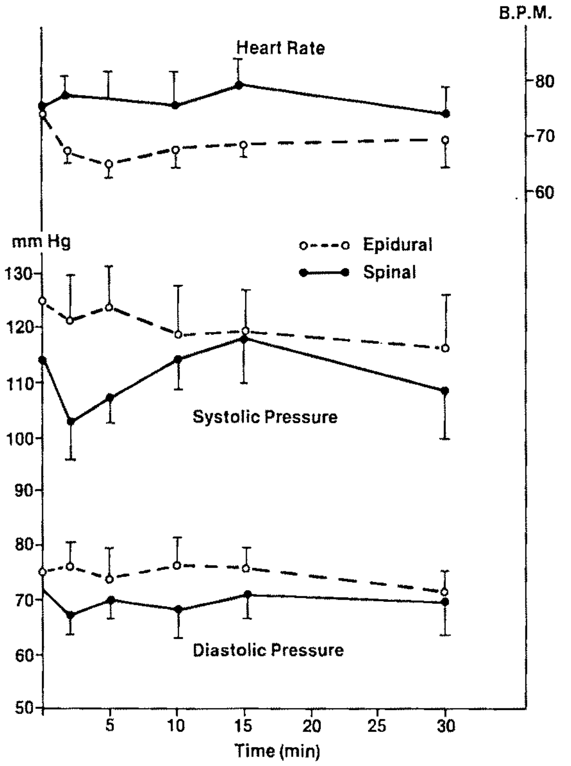

FIG 2. Mean ± SE heart rate (upper curve), systolic pressure (middle curve), and diastolic pressure (lower curve) following epidural or subarachnoid injection.

pooled for comparison with data for the patients in whom lidocaine was injected into the epidural space.

Discussion

The results of this study indicate that the initial rate of vascular absorption of lidocaine is less following injection into the subarachnoid space as compared to epidural administration. However, no difference in the mean maximum venous plasma level was observed between the two techniques. The differential rate of absorption from the epidural and subarachnoid spaces probably is related to anatomical vascular differences between the two areas. The epidural space contains a dense venous plexus located in the anterior and lateral portions of the space. The veins that make up the epidural plexus are relatively large, thin walled, and lack valves. Solutions injected into the epidural space are directly exposed to a large vascular surface area that provides ideal conditions for rapid vascular absorption. On the other hand the epidural space is also rich in adipose tissue. Since most local anesthetics are lipid soluble, they may be sequestered in the epidural adipose tissue which would tend to retard their vascular absorption. Indeed, etidocaine, the most lipid soluble of all commonly used local anesthetics has been shown to have the slowest rate of absorption from the epidural space.[6]

The capillaries and venules in the subarachnoid space originate primarily within the spinal cord. The veins draining the spinal cord form a tortuous venous plexus in the pia mater. This plexus consists of two median longitudinal veins, two arterolateral veins, and two posterior longitudinal veins which ultimately drain into the internal vertebral venous plexi. Therefore, drugs injected into the subarachnoid space probably must diffuse from cerebrospinal fluid into the spinal cord and into nerve roots before vascular absorption occurs. This is consistent with the observation that anesthesia was evident in all patients within 2 minutes after subarachnoid administration of lidocaine. However, no lidocaine was detectable in eight of the 10 patients 2 minutes after injection. In fact, no measurable levels of lidocaine in blood were present in four of the patients until 10 minutes after the subarachnoid injection of this agent, although in all patients the maximum level of anesthesia was well established by this time.

The differences in rates of absorption of local anesthetics from the epidural and subarachnoid spaces are probably not related to the difference in the concentration and volume of anesthetic solutions that were employed for epidural and spinal anesthesia in this study. With spinal anesthesia, 1.5 ml of 5% lidocaine was injected whereas 3.75 ml of a 2% lidocaine solution was administered with epidural anesthesia. It has been demonstrated that the peak blood levels of lidocaine, irrespective of injection site, are dependent on total dose rather than concentration or volume.[1, 2, 6] Moreover, solutions injected into the subarachnoid space are immediately diluted, and this minimizes the difference between a 2% solution and 5% solution. This spinal lidocaine solution did contain 7.5% glucose. It is not known whether the baricity of anesthetic solutions alters their rate of vascular absorption.

The duration of spinal anesthesia is usually considered to be shorter than the duration of epidural anesthesia.[6] Anesthetic duration is dependent on maintaining a critical concentration of drug within the nerve fiber and the inherent affinity of the anesthetic agent to the membrane receptor site. Maintenance of a critical anesthetic concentration in the nerve fiber is related to the amount of drug administered and to the rate at which anesthetic molecules are transported away from the injection site. Relatively small doses of anesthetic drugs are employed for spinal anesthesia.

For example, 300 to 500 mg of lidocaine administered epidurally is required to provide the same depth of anesthesia that can be achieved with the subarachnoid administration of 50 to 100 mg of lidocaine. The shorter duration of spinal anesthesia probably reflects the small dose of anesthetic agent employed and the inherent dilutional effect of the cerebrospinal fluid which will tend to further reduce the critical anesthetic concentration at the site of injection. Vascular absorption also will tend to reduce the critical anesthetic concentration. However, the data obtained in this study do not support the concept that the shorter duration of spinal anesthesia is related to a rapid rate of vascular absorption from the subarachnoid space.

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Baroreceptor Dysfunction after Carotid Endarterectomy

Hemodynamic data from 100 consecutive carotid endarterectomies revealed three distinct postoperative blood pressure responses. A hypotensive response affected 28 patients in whom mean arterial pressure decreased from 168 ± 29/90 ± 15 mm Hg before operation to 110 ± 21/68 ± 16 mm Hg after operation ($p < 0.001$). Maximum hypotension occurred 5.3 hours after endarterectomy. The pulse rate decreased significantly after operation. A hypertensive response affected 19 patients in whom mean blood pressure rose from 160 ± 29/87 ± 15 to 223 ± 32/110 ± 22 mm Hg ($p < 0.001$). Maximum hypertension was noted 2.3 hours after endarterectomy. This was unaccompanied by significant pulse changes. Fifty-three patients remained normotensive. Their preoperative blood pressure (150 ± 21/88 ± 12 mm Hg) was unaltered by carotid endarterectomy (149 ± 25/87 ± 14 mm Hg). Fluctuations in pressure did not correlate with age, indication for operation, or degree of ipsilateral and contralateral carotid arterial stenosis. Postendarterectomy hypotension and hypertension appear to represent transient baroreceptor dysfunction. (*Bove EL, Fry WJ, Gross WS, et al: Hypotension and hypertension as consequences of baroreceptor dysfunction following carotid endarterectomy. Surgery 85:633–637, 1979*)

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Duration of Bupivacaine Intradermal Anesthesia When the Bupivacaine Is Mixed with Chloroprocaine

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KIM, J.-M., GOTO, H., AND ARAKAWA, K.: Duration of bupivacaine intradermal anesthesia when the bupivacaine is mixed with chloroprocaine. Anesth Analg 58:364–366, 1979.

In a double-blind trial in 20 human volunteers, the duration of intradermal anesthesia with a mixture of bupivacaine, 0.5 mg, and chloroprocaine, 3 mg, was compared with the duration of intradermal anesthesia obtained with either bupivacaine, 0.5 mg, or chloroprocaine, 3 mg, alone. The duration of intradermal anesthesia produced by the bupivacaine mixed with chloroprocaine, 36 ± 16 (mean ± 1 SD) minutes, was significantly less than the duration of the same amount of bupivacaine alone, 139 ± 78 minutes. Duration of anesthesia with chloroprocaine alone, 24 ± 11 minutes, was similar to the duration of anesthesia with chloroprocaine plus bupivacaine. A possible explanation for these results is that bupivacaine competes with chloroprocaine for nonspecific receptors at the biophase and in the surrounding nerve tissue.

Key Words: ANESTHETICS, Local: bupivacaine; ANESTHETICS, Local: chloroprocaine; INTERACTIONS (DRUG): local anesthetics; ANESTHESIA, Duration: local anesthetics.

LOCAL anesthetics with short duration but rapid onset are often combined with long-acting anesthetics to compensate for the slow onset of action of the latter. A review of previous studies of local anesthetic mixtures used for this purpose indicates that while rapid onset has been a consistent finding, the duration of action has been inconsistent.

For example, comparison of a mixture of bupivacaine, 100 mg, plus chloroprocaine, 300 mg, with bupivacaine, 150 mg alone in brachial plexus block, reveals that the mean duration of motor blockade was 5 hours for the mixture compared to 7 hours after bupivacaine alone.[1] When tetracaine is added to procaine or lidocaine, the duration of epidural anesthesia appears to depend upon the dose of tetracaine. If the mixture contains 0.1% tetracaine and either 2% procaine or 1% lidocaine, half of a series of dogs studied had a duration of anesthesia as short as that observed when either procaine or lidocaine alone were used. The other half had anesthesia lasting as long as that produced by tetracaine alone. When the tetracaine concentration in the mixture was doubled, the duration of anesthesia was the same in all dogs as that observed when tetracaine was administered alone.[2]

Our clinical trials of a mixture of chloroprocaine and bupivacaine for regional blocks suggested that the duration of blockade was shorter than the same block accomplished using bupivacaine alone. This clinical impression prompted the present study.

Methods

A double-blind study was performed on 20 healthy young volunteers. The Human Subjects Committee of the University of Kansas Medical Center approved

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the study. Informed consent was obtained from each volunteer.

Using a tuberculin syringe, intradermal wheals were raised on the volar aspect of each volunteer's forearm with 0.2 ml of three local anesthetic solutions. The first was 1.5% chloroprocaine, 3 mg; the second was 0.25% bupivacaine, 0.5 mg; and the third was a mixture of equal volumes of 3% chloroprocaine, 3 mg, and 0.5% bupivacaine, 0.5 mg. Commercially available local anesthetics without preservatives were used. Three percent chloroprocaine was diluted with normal saline to make 1.5% chloroprocaine. Following the injections, analgesia to pinprick on the injection site was determined every 10 minutes until full recovery occurred. The duration of analgesia was measured from the time of injection to the last reported analgesia at the site. Statistical analysis was performed using the Student's *t* test for paired data. Results are expressed as means ± standard deviations.

Results

The mean duration of intradermal analgesia was found to be 24 ± 11 (mean ± 1 SD) minutes with 1.5% chloroprocaine, 139 ± 78 minutes with 0.25% bupivacaine, and 36 ± 16 minutes with the combination of the two local anesthetics (Table). The difference in duration between the plain and compounded bupivacaine is 103 minutes, compared to only 12 minutes difference between the chloroprocaine and mixture of chloroprocaine plus bupivacaine.

Statistical analysis revealed that the difference in duration of action between bupivacaine alone and bupivacaine plus chloroprocaine was highly significant ($p < 0.001$), and that the difference in duration of action between bupivacaine-chloroprocaine mixture and chloroprocaine alone was also significant ($p < 0.01$).

Discussion

According to Tucker and colleagues,[3] factors potentially influencing the duration of local anesthesia include: (1) intrinsic binding of drug to receptors in the nerve membranes, (2) nonspecific binding of drug to membranes or proteins near the site of action, (3) penetrability of drug through diffusion barriers to the biophase, and (4) effect of the drug on local tissue perfusion.

TABLE

Duration of Intradermal Anesthesia Obtained by Chloroprocaine Alone, Bupivacaine Alone, and a Mixture of Chloroprocaine and Bupivacaine

Conc. of active agent in solution (%)			
Chloroprocaine (pKa 8.66)	Bupivacaine (pKa 8.1)	pH	Min of duration (mean ± 1 SD)
1.5		3.37	24 ± 11
	0.25	5.86	139 ± 78
1.5	0.25	3.44	36 ± 16

The main sensory receptors for cutaneous pain are naked nerve endings. Intradermal local anesthetics are readily accessible to these nerve endings; the ability of the agent to penetrate to the site of action is therefore of minor importance.[4]

In our study of intradermal anesthesia, the duration of bupivacaine was significantly shortened when it was added to chloroprocaine. A significant difference between the mixture and bupivacaine alone is the acidity of the solution.

The pH range of commercially available chloroprocaine is 3.0–3.5 (Penwalt Pharmaceutical Company, Personal communication). When bupivacaine, pH 5.86, is mixed with chloroprocaine, the pH of the resulting mixture was 3.44 in our study. A similar low pH of the same mixture was observed by Brodsky and Brock-Utne.[5] pH data cannot be averaged until they have been converted back to real hydrogen ion concentration.[6] After the pH data of bupivacaine, 5.86, and chloroprocaine, 3.37, are converted to real hydrogen ion concentrations, the calculated pH value of the resulting mixture of these two solutions is 3.67. The difference of 0.23 unit between the calculated and measured pH values could be the result of an error during mixing. Both bupivacaine and chloroprocaine should be almost completely ionized at this pH. Rapid onset of intradermal anesthesia even with almost completely ionized local anesthetics supports the thesis that penetrability of the drug through diffusion barriers is not an important factor; therefore, the amount of available local anesthetics at the nerve membrane and thus the duration of action should not be affected by the acidity.

Tissue binding of bupivacaine could be affected by acidity and also by the presence of chloroprocaine. Tissue binding could be specific to the receptors in the nerve membrane, if present, or could be nonspecific. Little is known of the relationship between local anesthetic effect and drug concentration in the biophase or even in the affected tissue. However, there is a good correlation between protein binding and duration of anesthesia.[3] Greater protein binding capacity implies that the drug should bind to a greater degree with the protein component of nerve membranes, and, thus, be associated with a longer duration of action. Since this binding is nonspecific, many drugs with similar physicochemical characteristics compete with each other. Diphenylhydantoin, quinidine, meperidine, and desipramine, for example, cause displacement of bupivacaine in plasma.[7] Also the percentage of plasma protein binding of local anesthetics is inversely related to the hydrogen ion and to the local anesthetic concentrations.[8, 9] Nishimura and colleagues[9] reported that protein binding capacity of chloroprocaine is consistently higher than that of bupivacaine within the pH range of 5–9 and within the range of local anesthetic concentrations 1–20 μg/ml in 4% solutions of bovine serum albumin.

Luduena[10] reported that the duration of intradermal block with 0.25% propoxycaine, a long-acting local anesthetic, in guinea pigs is significantly shortened when propoxycaine is added to 2% procaine. The possible explanation given was that the high concentration of the procaine in the mixture competes for nonspecific receptors for which the difference in affinity may be small. The amount of propoxycaine not bound to receptors and thus liable to systemic absorption would be increased, thereby shortening the duration of the anesthesia.

If the systemic absorption of one local anesthetic is facilitated by when it is added to another local anesthetic, blood concentrations of the local anesthetic more susceptible to absorption would rapidly reach higher peak levels following injection for major regional anesthesia. However, a study reported by Raj and associates,[11] showed that the peak arterial plasma level of bupivacaine following epidural and brachial plexus blocks with bupivacaine mixed with either chloroprocaine or lidocaine was comparable to that of bupivacaine used singly for the same blocks. Wilkinson and Lund[12] suggested that the long duration of bupivacaine could be due to its slow removal from the biophase and surrounding nerve tissue which is irrespective of the rate of overall elimination from the body. These reports[11, 12] suggest that systemic vascular absorption is not facilitated nor is tissue perfusion increased in the affected tissue by mixing bupivacaine with chloroprocaine and that the biophase and immediate surrounding nerve tissue are the most probable sites of competition for nonspecific receptors.

In conclusion, if competition for nonspecific receptors is responsible for the short duration of the compounded bupivacaine in our intradermal study, the biophase and surrounding nerve tissue are the most likely sites for the competition. The difference in duration of blockade between chloroprocaine and the chloroprocaine-bupivacaine mixture is only 12 minutes; this may be compared to a difference in duration of 103 minutes between bupivacaine alone and the bupivacaine-chloroprocaine mixture. This also supports the possibility that drug interaction occurs in or near the biophase.

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ANESTH ANALG
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Muscle Contractures and Adenosine Triphosphate Depletion in Porcine Malignant Hyperthermia

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GRONERT, G. A.: Muscle contractures and adenosine triphosphate depletion in porcine malignant hyperthermia. Anesth Analg 58:367–371, 1979.

This study compares several methods for diagnosing susceptibility to malignant hyperthermia, using two groups of Poland China swine narrowly defined as genetically susceptible or normal (five pigs each) depending respectively on their response to halothane or to halothane and succinylcholine. Vastus medialis muscle biopsies were excised under thiopental-N_2O-O_2 anesthesia and used for examination of (1) contracture responses to halothane, (2) contracture responses to caffeine and halothane-caffeine, and (3) adenosine triphosphate (ATP) depletion with and without halothane. All studies were performed in organ baths at 37 C.

Halothane alone produced contractures in two susceptible and one normal preparation; caffeine always produced a contracture at lower concentrations in susceptible muscle; caffeine-halothane contractures in susceptible muscle occurred at lower mean caffeine concentrations, but there was some overlap of individual values; mean ATP depletion was greater in susceptible muscle, but with considerable overlap.

Comparisons with the findings of others were hampered by use of absolute rather than comparative values for tension, e.g., grams, rather than grams per cross-sectional area or fraction of peak tension. Examination of the complete dose-response curve provided the best comparative information and caffeine was the consistent predictor of susceptibility.

Key Words: HYPERTHERMIA, Malignant.

ELECTRICAL and mechanical properties of human skeletal muscle are difficult to examine because of the unavailability of viable intact (tendon to tendon) fiber preparations. Fragment biopsies of human skeletal muscle provide a feasible alternative,[1] and their contracture responses were proposed by Kalow et al[2] as a means of differentiating normal individuals from those susceptible to malignant hyperthermia (MH). The early investigators of these contracture responses approached the problem differently and became divided between those who preferred halothane as the sole stimulating drug[3,4] and those who preferred caffeine and the combination halothane-caffeine.[2] However, regardless of drug preferences, confidence in the accuracy of contracture responses in evaluating susceptibility to MH must be based upon populations known to be susceptible or normal. Although this has been accomplished to a certain extent by study of survivors of MH and of individuals presumed to be normal, widely varying contracture responses have been reported for humans, and the limits between susceptible and normal are difficult to define.[5,6] This problem can be circumvented with the porcine model of MH by using rigid criteria to distinguish between susceptible and normal. Whereas most susceptible swine develop rigidity during a screening inhalation of halothane, some do not and hence appear to be normal, only to develop typical MH when exposed to both halothane and succinylcholine. Selection of swine for comparative investigations should consider and screen for these variations in genetic susceptibility.[7]

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Harrison et al[8] introduced muscle adenosine triphosphate (ATP) depletion as an adjunctive test of susceptibility, based upon the premise that the greater metabolism in MH muscle exposed to halothane results in a greater reduction in energy stores than that observed in normal muscle exposed to halothane. The present study examines three aspects of biopsy diagnosis of MH susceptibility—it compares the two methods of producing contractures by measuring responses to halothane, to caffeine, and to the combination halothane-caffeine; it compares two groups of littermate Poland China swine, narrowly defined as either susceptible or normal, depending, respectively, on their response to halothane or to halothane and succinylcholine;[9] it evaluates the measurement of ATP depletion.

Materials and Methods

Ten swine weighing 31 to 48 kg each were screened for susceptibility to MH by a 5-minute inhalation of 3% halothane; five developed hind limb rigidity and were identified as genetically susceptible to MH. On another day, the remaining five swine were further screened by an exposure to halothane and succinylcholine to rule out lesser degrees of susceptibility to MH. They were given thiopental, 10 to 15 mg/kg, and atropine, 0.4 mg IV, intubated, and ventilated with 50% nitrous oxide and oxygen so as to maintain arterial carbon dioxide tensions of 40 ± 2 torr. After that, ventilation was not changed. One percent halothane was then introduced and continued for 30 minutes, and, 15 minutes after halothane was begun, succinylcholine, 3 mg/kg IV, was given. Arterial blood gas and acid base samples were drawn at 10, 20, and 30 minutes. These five swine did not develop "runaway" metabolism, and satisfied the criteria suggested as normal by pilot studies: arterial carbon dioxide tension (P_{CO_2}) remained below 55 torr, and buffer base did not decrease more than 5 meq/L. Swine screened as described have not demonstrated inconsistent susceptibility upon re-exposure to triggering agents.

Several days later the pigs were re-anesthetized with thiopental and atropine, intubated and ventilated with nitrous oxide-oxygen, as before, to an arterial P_{CO_2} of 40 ± 2 torr, and a biopsy was excised from the vastus medialis muscle. Bundles were dissected into two specimens, 1.2 to 2 cm long, weighing 50 to 150 mg. The modified Krebs-Ringers solution in two 37 C organ baths contained: calcium, 2.5 mM, sodium, 134 mM, potassium, 4.6 mM, magnesium, 1.0 mM, chloride, 124 mM, bicarbonate, 16 mM; H_2PO_4, 1.2 mM, sulfate, 1.0 mM, and glucose, 11.1 mM. One bath was bubbled with a mixture of 95% O_2 and 5% CO_2 (carbogen), the other with carbogen plus 4% halothane. A roller pump was used to force the latter mixture into the organ bath.[10] During bubbling, the range for the bath pH was 7.40–7.45, for P_{CO_2}, 25–30 torr.

The fiber fragments were tied at each end with silk thread and mounted into the baths between flat platinum electrodes which were 5.7 cm long and 6 mm wide. Stimulation at 0.1 Hz, duration 2 to 10 msec, provided an estimate of viability. If there was no contractile response, the bundles were discarded and another biopsy taken. Viable bundles were stimulated at supramaximal voltage, tension was measured using a Statham or Grass transducer, and a length-tension curve was determined to identify the optimal length (l_o) of the preparation. Increases in passive tension (contracture) were particularly watched for in the halothane bath. When passive tension had stabilized to relatively constant values, caffeine, 98 mM, in Krebs-Ringer solution was pipetted into the 14-ml baths in amounts calculated to provide the following concentrations (bath concentrations verified on two occasions by a spectrophotometric technique). In the nonhalothane bath the caffeine concentrations were 0.5, 1, 2, 4, 8, 16, and 32 mM. In the halothane bath the caffeine concentrations were 0.25, 0.5, 1, 2, 4, 8, and 16 mM. Succeeding doses were injected either after 4 minutes, or 2 minutes after the observed contracture response reached a plateau. When contracture observations were complete, the length and weight of the muscle bundle between the silk ties were measured for calculation of cross-sectional area.

The remaining biopsy specimen was cut into pieces weighing 50 to 100 mg each and approximate 400-mg amounts were placed into two additional 37 C organ baths, one bubbled with carbogen, the other with carbogen-4% halothane. After 45 minutes, they were removed, blotted dry, quick-frozen and stored, and later assayed for ATP and creatine phosphate.[11] To prevent hydrolysis of ATP due to warming, the frozen samples were prepared in a refrigerated environmental chamber (−25 C), and the assay was continued with the samples cooled in dry ice. Results are expressed as means ± standard error; intergroup comparisons were determined from the unpaired Student *t*-test, $p < 0.05$ considered significant.

Results

Both caffeine and caffeine-4% halothane contractures were different between susceptible and nonsusceptible animals, based upon mean values (Figure). There was no overlap between values in the caffeine-alone group, i.e., all normal contracture responses occurred at concentrations of caffeine that were greater than those for all susceptible responses. Caffeine-4% halothane was not as precise, in that some normal contracture responses occurred at concentrations of caffeine that were equal to or less than those for some of the susceptible responses. Halothane stimulated tension in susceptible muscle in the absence of caffeine, in that passive tensions at optimal length (l_o) were greater (Figure). Actual l_o values for tension were 1.2 ± 0.1 g and 2.2 ± 0.4 g without and with halothane, respectively, in susceptible muscle, and 1.4 ± 0.1 g and 1.7 ± 0.2 g without and with halothane in normal muscle. However, obvious contractures in response to halothane alone were observed on only three occasions—twice in muscle from susceptible swine and once in muscle from a normal swine; these contractures were not different in amplitude or pattern, and they decreased in tension when halothane was briefly discontinued.

The ATP depletion test was a valid measure of susceptibility based upon mean values (Table) but there again was overlap of individual values. Measurements of creatine phosphate were not useful as a screening method. Values for ATP were less in susceptible as compared to normal muscle; values for creatine phosphate were not significantly different.

TABLE

Muscle Energy Stores for 45-Minute Incubation at 37 C (mean ± SE)

	4% Halothane	No halothane	Ratio
ATP (μmol/g)			
Normal	2.29 ± 0.13	2.28 ± 0.14	1.00
Susceptible	1.40 ± 0.09*†	1.73 ± 0.12†	0.81†
Creatine phosphate (μmol/g)			
Normal	9.69 ± 2.15	11.31 ± 2.19	0.86
Susceptible	5.39 ± 1.14	6.71 ± 1.33	0.80

* Different from no halothane ATP value, $p < 0.05$.
† Different from normal, $p < 0.05$.

Discussion

Interpretation of the present data in relation to those of others is hampered by the various means of expressing the data. The key to the diagnosis of susceptibility is the demonstration of increased sensitivity to the contracture-producing drug, as in the Figure, caffeine, or halothane-caffeine. This involves measurement of a dose-response, or concentration-response curve. The ambiguities arise from the units for the ordinate. Most authors express this in grams of tension,[2, 4, 7, 12–15] and Kalow et al[5, 6] further focus our attention on the importance of the initial rise of the curve by defining a caffeine-specific concentration: that concentration of caffeine that increases contracture tension 1 g. While either tension in grams or caffeine specific concentration may be particularly useful for comparing responses within one's own laboratory, these measures may be misleading when analyzing the results of other laboratories. In our laboratory, using l_o, thicker muscle bundles tend to develop 1 g of tension sooner (have a lower caffeine specific concentration) than do thinner bundles; yet their dose response curves are virtually identical when tension is expressed as grams per square centimeter or as fraction of peak tension. Also, use of the caffeine-specific concentration provides only one value for comparison, and one does not know its position on the complete dose-response curve. Finally, Kalow et al's range for caffeine-specific concentrations in normal humans varies markedly. On one occasion, they define their lower limit of normal caffeine responses as approximately 8 mM.[5] Yet in that same study, a group of six incidental biopsies from normal patients (reference 5, figure 1—clear symbols above the abscissa for values of caffeine 5 to 8 mM) developed 1 g of tension at 5 to 8 mM caffeine, well within Kalow and Britt's range of susceptibility. Elsewhere (reference 16, figure 1) normal responses to caffeine are shown at the other extreme, e.g., 32 mM. It is not surprising, then, that these normal values on occasion overlap values from susceptible muscle.[5, 6]

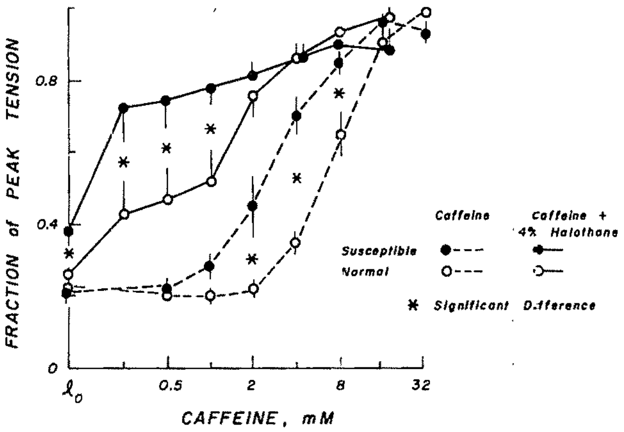

FIGURE. Abscissa: concentration of caffeine on a log scale. Ordinate: passive tension, expressed as fraction of peak tension, of vastus medialis fragment muscle biopsies from normal or susceptible swine, mean ± SE, 37 C.

It seems advisable to express tension (a historically acceptable but erroneous term since it really refers to stress—grams per square centimeter—rather than to tension—grams per centimeter) in a manner that allows for differences in fiber cross-sectional area and to show these as a classical pharmacologic dose-response curve. The present data were expressed as tension in grams, in grams per square centimeter, and as fraction of peak tension. All three methods yielded similar relative values, but the last was generally most useful for comparisons with our and others' porcine and human data. Also, examination of the entire dose-response curve, rather than of a single tension value at a single drug concentration, provided more definitive information about the pattern of response of a particular preparation. This reasoning is supported by the report of Okumura et al,[7] who, using a variety of screening tests, reported diagnostic accuracy when comparing dose-response curves, but some degree of overlap when the data were compared at single concentrations of triggering agents.

In the present study, caffeine reliably and unambiguously produced muscle contractures at lower concentrations in muscle from susceptible swine than in muscle from normal swine, supporting the findings of others[7, 12, 13, 15] that this is a valid method for screening porcine susceptibility. Although our mean values were significantly different following caffeine and halothane combined, individual results sometimes overlapped. Overlap has been noted with a variety of screening techniques,[7] and the causes may not be obvious. Halothane 4% depresses muscle contractile activity,[17] but comparative contracture studies are possible at 4%[15] and even at 5% halothane.[17] In addition, lower concentrations of halothane are less effective in stimulating caffeine contractures.[17] We have not formally examined the efficacy of lower concentrations of halothane in determining porcine susceptibility, but casual observations suggest findings similar to the present study. Halothane apparently shifts the dose-response curve of normal muscle more than that of susceptible, with consequent greater overlapping of individual responses.

Measurements of contracture responses to halothane by itself present greater problems in interpretation, as similar contractures occurred in both normal and susceptible muscle. Whereas Moulds and Denborough,[4] Okumura et al,[7] Ellis et al,[3, 14] Nelson et al,[12] and Anderson et al[15] believe that halothane contractures are reliable in diagnosing susceptibility, Kalow et al[5, 6] apparently do not. Nelson et al[12] observed that contractures did not occur in susceptible muscle at 25 C and explained Kalow et al's[5] results as being due to testing at this temperature. The present study at 37 C supports the results of Kalow et al. Okumura et al[7] demonstrated increasing contracture responses of susceptible muscle with the addition of up to 3% halothane, and one would thus expect 4% halothane, despite its being more depressant than the usual clinical concentrations, to also be more likely to result in contractures in the absence of caffeine than would lesser concentrations of halothane.

Whereas the rigorous screening techniques used in this and other studies[7] to distinguish normal from susceptible swine enabled careful examination of the utility of contracture responses in evaluation of susceptibility, it is highly unlikely that similar well defined normal and susceptible groups can be studied in humans who are genetically closely related. As a result the reliability of these contracture tests in humans would depend critically on the precise definition of the range of responses of normal human skeletal muscle to these drugs. Variables to be carefully controlled, insofar as is possible, include age, specific muscle, anesthetic agents, consistently identical handling and viability. Kalow et al[6] have reported that normal human muscle bundles from various different muscles have similar contracture responses to caffeine and to halothane-caffeine, but susceptible muscle could be considerably more variable in its patterns of response. It seems advisable to limit the biopsy site in humans to muscles expected to be consistently and markedly involved, such as as the quadriceps.

Measurements of ATP depletion were more variable than the incidence of halothane contractures. The mean differences were significant but small, there was considerable overlap, and it was difficult to evaluate individual results. Measurements of creatine phosphate were even less reliable. However the actual values for ATP, with or without halothane, were lower in susceptible than in normal muscle. Such differences, i.e., actual ATP values, might provide a comparison between normal and susceptible, based upon the presumption that, since the bath provides substrates, normal muscle would maintain its energy stores, while susceptible muscle would be unable to counter the depletion due to increased metabolism. But the central core of the muscle is likely poorly supplied with oxygen and other substrates, and the muscle bundles may be damaged during preparation; assay values are thus skewed downward a variable amount depending upon these factors. Also, low values may be seen in normal muscle if there is a delay from the time of biopsy to the time of beginning the ATP depletion studies, with a resulting depletion of creatine phosphate, leaving inadequate stores for maintenance of ATP levels. Results in studies of swine by Harrison et al[8] and Nelson et al,[18] and Britt et al's[19] experience in humans suggest that the ATP depletion ratio is a valid differentiating test, but the reasons for the differences between their and our data are elusive.

In summary, caffeine-induced skeletal muscle contractures on muscle fragments were valid in determining susceptibility to MH in swine, particularly when the data were expressed as a concentration-response curve. Contractures induced by the combination of halothane and caffeine, by halothane alone, or by measurements of ATP depletion were less reliable. Similarities between porcine and human MH suggest that contracture responses may be reliable screening tests in humans, but there are interlaboratory differences in results relating to various drugs that remain unexplained. Problems in defining the lower limits of drug sensitivity in normal muscle and variations in expression of data may have complicated the interpretation of human results.

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Cardiovascular Responses to Clamping of the Aorta during Epidural and General Anesthesia

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LUNN, J. K., DANNEMILLER, F. J., AND STANLEY, T. H.: Cardiovascular responses to clamping of the aorta during epidural and general anesthesia. Anesth Analg 58:372–376, 1979.

The cardiovascular responses of aortic cross-clamping and declamping with normal and high ventricular filling pressures were compared during epidural and nitrous oxide-morphine anesthesia in 32 male patients undergoing reconstructive aortic surgery. The patients were divided into four groups. Groups I and II had lumbar epidural blocks with bupivacaine and received nitrous oxide in oxygen to breathe; groups III and IV were anesthetized with morphine (2 mg/kg) and nitrous oxide. During aortic occlusion groups I and III received Ringer's lactate at a rate which maintained mean pulmonary capillary wedge pressure ($\overline{\text{PCWP}}$) 3 to 4 torr above pre-anesthetic values whereas groups II and IV were given Ringer's lactate rates which kept $\overline{\text{PCWP}}$ similar to pre-anesthetic values. Prior to cross-clamping mean arterial blood pressure and systemic vascular resistance were lower in groups I and II than in groups III and IV but cardiac output, $\overline{\text{PCWP}}$, and pulmonary vascular resistance were similar in the four groups. Cross-clamping of the aorta produced no significant change in any cardiovascular variable measured in any group. Declamping did not significantly alter any variable in groups I and III but produced moderate hypotension in group IV and severe hypotension in group II as well as significant decreases in $\overline{\text{PCWP}}$ in both groups. Our data demonstrate that aortic cross-clamping and release result in little change in cardiovascular dynamics in patients anesthetized with epidural or morphine-nitrous oxide and given balanced salt solutions intravenously in amounts adequate to increase left ventricular filling pressures prior to release of the aortic cross-clamp. Our findings also indicate that hypotension can occur in patients in whom left ventricular filling pressures are maintained at normal levels prior to cross-clamp release, especially in patients given epidural anesthesia.

Key Words: SURGERY, Cardiovascular; ANESTHETIC TECHNIQUES, Epidural; ANESTHETIC TECHNIQUES, Intravenous morphine.

AORTIC cross-clamping and declamping during reconstructive aortic surgery is usually well tolerated but occasionally may produce severe hemodynamic disturbances.[1] Unfortunately, few data are available regarding the influence of anesthesia or operative volume replacement on cardiovascular dynamics during aortic occlusion and subsequent release. The object of this investigation was to compare the cardiovascular responses of aortic cross-clamping and declamping with normal and high ventricular filling pressure during epidural and nitrous oxide-morphine anesthesia.

Methods

A total of 32 male patients, A.S.A. class II–IV, 48 to

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76 years of age, weighing 60 to 90 kg each, and about to undergo major vascular surgery involving the distal aorta were the experimental subjects. Twenty-seven patients had essential hypertension (systolic blood pressures >150 torr) and were being treated with a variety of antihypertensive medications. The experimental subjects were randomly divided into four groups.§ Sixteen of the patients (groups I and II) received a bupivacaine lumbar epidural block prior to breathing nitrous oxide and oxygen. Sixteen additional patients (groups III and IV) were given general anesthesia with morphine sulfate (2 mg/kg) plus nitrous oxide.

Written informed consent was obtained from each of the patients at the time of the preoperative visit. All patients were premedicated with morphine sulfate (0.1 mg/kg) and scopolamine (0.5 mg) intravenously 90 minutes prior to the scheduled time of operation. Upon arrival in the induction room, the patients were continuously monitored with a lead V_5 EKG while catheters were placed in a hand vein and a radial artery. Prior to inducing anesthesia, a thermodilution flow-directed balloon-tipped pulmonary artery catheter (Edwards Quadruple Lumen Thermodilution, model no. 93A-131-7F) was percutaneously introduced into the pulmonary artery (PA) through the right internal jugular vein using a Cordis introducer. While in the left lateral position, group I and II patients had a 22-guage epidural catheter placed securely in the L_{3-4} epidural space with the aid of an 18-gauge Tuohy needle. The patients were then placed in the supine position and after breathing 100% oxygen through a face mask for 15 minutes, 20 to 25 ml of a 0.5% bupivacaine solution were injected through the epidural catheter. Following this, the patients were given thiopental (3 to 4 mg/kg) and succinylcholine (2 mg/kg) intravenously and the trachea was intubated with a cuffed Murphy endotracheal tube. Respirations were mechanically controlled with 60% nitrous oxide in oxygen at a rate of 10 to 15 breaths per minute using a semi-closed circle system. In this fashion Pa_{CO_2} was maintained at 35 to 40 torr throughout the study as measured in radial arterial blood every 10 minutes. Additional venous blood was obtained for serum potassium determinations with each arterial blood gas sample. Additional bupivacaine (10 to 15 ml of the same solution) was administered every 2 hours throughout the operative procedure.

In groups III and IV anesthesia was induced with intravenous morphine sulfate administered at a rate of 8 to 10 mg/min while the patients were breathing 100% oxygen. Respirations were controlled at 10 to 15 breaths per minute using a face mask and a semiclosed circle system. After 2 mg/kg of morphine had been administered, the patients were given thiopental (1 to 2 mg/kg IV), paralyzed with succinylcholine (2 mg/kg IV), and the trachea was intubated with a cuffed Murphy endotracheal tube. Following this, the inspired mixture of gases was changed to 60% nitrous oxide in oxygen. Respirations were mechanically controlled in a similar fashion as in groups I and II. Muscle relaxation was obtained using pancuronium bromide (6 mg IV slowly) in patients in groups III and IV. Paralysis was maintained with 1 to 3 mg of pancuronium every 45 to 60 minutes throughout the surgical procedure and monitored with a nerve stimulator. Muscle relaxants were not required in groups I and II.

The operations in this study were performed in a similar fashion by the same surgeon and surgical team. Application of the aortic cross-clamp was instantaneous; however, release was accomplished over 4 to 5 minutes. Prior to cross-clamping, Ringer's lactate was administered in all groups at a rate necessary to maintain pulmonary capillary wedge pressure at pre-anesthetic levels. During the period of aortic occlusion groups I and III received Ringer's lactate at a rate which maintained mean pulmonary capillary wedge pressure (PCWP) 3 to 4 torr above pre-anesthetic values, whereas groups II and IV were given the solution at rates which kept PCWP at preanesthetic values. Esophageal temperature was measured using a Yellow Springs thermistor. Arterial blood gases were measured with an Instrument Laboratories blood gas analyzer and corrected to 37 C. Serum potassium levels were measured with an Instrument Laboratories flame photometer.

The study consisted of obtaining cardiovascular dynamics in all groups of patients 5 minutes before aortic cross-clamping (control),‖ 5 minutes after cross-clamping the aorta, and 5 minutes before and after aortic clamping was completely released. Arterial and venous blood samples for blood gas analysis and serum potassium determination were obtained following each set of cardiovascular recordings. Cardiovascular dynamics measured during this investigation included cardiac output (CO) measured in liters per minute, mean arterial ($\overline{\text{BP}}$) and pulmonary capillary wedge ($\overline{\text{PCWP}}$) pressures (torr) systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). SVR and PVR (measured in dynes•sec/cm^5) were calculated using standard formulas:

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§ Technically, randomization ceased when the study was half finished, at which point it was decided not to place any more patients in group II because of the danger of hypotension. For the remainder of the study patients randomly picked to be in group II were placed in group I instead.

‖ This time averaged 97 ± 17 minutes after induction of anesthesia and was similar in all groups.

$$\text{SVR} = \frac{\overline{\text{BP}} - \overline{\text{RAP}}}{\text{CO}} \times 80$$

$$\text{PVR} = \frac{\overline{\text{PAP}} - \overline{\text{PCWP}}}{\text{CO}} \times 80$$

Cardiac output was measured by an Edwards computer thermodilution technique using the balloon-tipped flow-directed thermodilution pulmonary artery catheter and 10 ml of 0 C saline for each injection. Pressures were recorded continuously on a Hewlett-Packard multi-channel recorder.

Data were analyzed for statistical significance utilizing Student's paired *t*-test for comparison of changes from control and Student's unpaired *t*-test for comparison between groups; $p < 0.05$ was considered significant.

Results

There were 12, 4, 10, and 6 patients in groups I to IV, respectively. All groups were comparable with respect to age, weight, and systemic disease (Table 1). The average aortic cross-clamp time was comparable in all groups. Sensory levels of anesthesia prior to administration of thiopental in groups I and II, as determined by pinprick stimulation, were T_2-T_4. Pa_{O_2} was above 100 torr and serum potassium levels were between 4 and 5 meq/L in all groups throughout the procedure. Estimated blood loss did not exceed 600 ml prior to aortic release in any patient.

Control (prior to cross-clamp but after anesthetic induction) mean arterial blood pressures and SVR were lower in patients in groups I and II than in patients in groups III and IV (Table 2); however, control CO, $\overline{\text{PCWP}}$, and PVR were similar in all groups. Prior to cross-clamping groups I and II required 2853 ± 239 and 2500 ± 219 ml of lactated Ringer's solution, respectively, to maintain $\overline{\text{PCWP}}$ at pre-anesthetic values (Table 1). In contrast, group III and IV required significantly less intravenous fluid during this interval (group III = 1625 ± 172 ml, group IV = 1581 ± 164 ml). Aortic cross-clamping produced no significant change in any variable measured in any of the groups (Table 2). During cross-clamp, patients in group I received significantly greater volumes of lactated Ringer's solution than patients in all the other groups (Table 1). Prior to cross-clamp release $\overline{\text{PCWP}}$ was significantly greater in groups I and III than groups II and IV.

Release of aortic occlusion resulted in no change in any variable in groups I and III but significantly decreased $\overline{\text{BP}}$ and $\overline{\text{PCWP}}$ in groups II and IV. Decreases in $\overline{\text{BP}}$ and $\overline{\text{PCWP}}$ in group II were greater than in group IV. Indeed, two of the four patients in group II had 2 to 3 mm ST-segment depression on the EKG with declamping. Because of the dramatic decreases in $\overline{\text{BP}}$ in group II, only four patients were studied during this investigation.

One patient in group I and three in group III experienced transient premature ventricular contractions when the aorta was cross-clamped. There was no evidence of ST-segment depression with aortic cross-clamping in any group.

Discussion

The results of this study demonstrate that aortic cross-clamping and release produce insignificant changes in cardiovascular dynamics with either epidural or morphine-nitrous oxide anesthesia, provided left ventricular filling pressures are maintained at 3 to 5 torr above pre-cross-clamp values prior to declamping. Our data also indicate that with $\overline{\text{PCWP}}$ at pre-anesthetic values during aortic cross-clamp, release of occlusion results in minimal hypotension in patients anesthetized with general anesthesia but marked de-

TABLE 1

Preoperative and Intraoperative Data (mean ± SD)

Group	Age	Weight	Ringer's lactate infused prior to cross-clamping	Ringer's lactate infused during aortic occlusion	Cross-clamp time
	yr	*kg*	*ml*	*ml*	*min*
I	64 ± 9	85 ± 8	2853 ± 239	1346 ± 154	88 ± 16
II	68 ± 8	83 ± 7	2500 ± 219	846 ± 91*	94 ± 19
III	63 ± 8	90 ± 9	1625 ± 172*	972 ± 101*	108 ± 21
IV	71 ± 9	72 ± 12	1581 ± 164*	463 ± 65*·†	99 ± 18

* $p < 0.05$ using Student's unpaired *t*-test when compared to group I values.

† $p < 0.05$ using Student's unpaired *t*-test when compared to group III values.

TABLE 2
Cardiovascular Responses to Aortic Occlusion during General and Epidural Anesthesia (mean ± SD)

Response by group	Before cross-clamping	After cross-clamping	Before cross-clamping release	After cross-clamping release
$\overline{\text{BP}}$ (torr)				
I	73 ± 8	77 ± 6	84 ± 7	74 ± 6
II	78 ± 7	81 ± 8	76 ± 8	50 ± 7†
III	100 ± 8†	100 ± 6†	95 ± 6†	87 ± 8†
IV	96 ± 9‡	102 ± 8‡	90 ± 7‡	78 ± 9‡
CO (L/min)				
I	4.1 ± 0.6	3.8 ± 0.6	3.6 ± 0.7	3.8 ± 0.6
II	3.7 ± 0.7	3.6 ± 0.7	3.5 ± 0.5	3.4 ± 0.6
III	3.6 ± 0.6	3.1 ± 0.5	3.3 ± 0.6	3.6 ± 0.7
IV	4.1 ± 0.5	3.6 ± 0.6	3.6 ± 0.7	3.6 ± 0.7
PCWP (torr)				
I	12 ± 2	15 ± 3	17 ± 2*	14 ± 2
II	14 ± 2	15 ± 2	11 ± 2†	3 ± 2*†
III	13 ± 1	13 ± 2	17 ± 2*§	15 ± 3§
IV	13 ± 2	13 ± 2	10 ± 2	8 ± 2*
SVR (dynes·sec/cm^5)				
I	1311 ± 214	1379 ± 174	1636 ± 192	1329 ± 183
II	1396 ± 173	1411 ± 178	1306 ± 159	921 ± 196*†
III	2438 ± 186†	2586 ± 189	2390 ± 178†	2096 ± 206§
IV	1927 ± 184‡	2071 ± 152‡	1856 ± 181‡	1422 ± 166*‡
PVR (dynes·sec/cm^5)				
I	136 ± 17	167 ± 15	168 ± 16	149 ± 13
II	137 ± 15	149 ± 20	141 ± 15	119 ± 18
III	101 ± 14	154 ± 19	156 ± 14	136 ± 17
IV	121 ± 17	157 ± 19	139 ± 17	132 ± 15

* $p < 0.025$ using Student's paired t-test when compared to control values.
† $p < 0.05$ using Student's unpaired t-test when compared to group I values.
‡ $p < 0.05$ using Student's unpaired t-test when compared to group II values.
§ $p < 0.05$ using Student's unpaired t-test when compared to group IV values.

creases in mean arterial pressure in patients anesthetized with epidural anesthesia. Our findings suggest that patients in whom left ventricular filling pressure has been increased by infusion of balanced salt solutions prior to aortic release have greater cardiovascular stability after aortic cross-clamping.

Cross-clamping of aortic blood flow is a requirement for surgery of the distal aorta and its branches. Abrupt cessation of aortic blood flow may produce alarming increases in aortic blood pressure and overt left ventricular failure.[2] On the other hand, abrupt release of aortic occlusion has been known to produce severe hypotension, sometimes resulting in hypovolemic shock and death.[3] In this study, no patient experienced severe hypertension during aortic cross-clamping. However, in those patients in whom no attempt was made to expand the intravascular volume prior to aortic declamping, significant hypotension occurred with release of aortic occlusion.

Many investigators report significant increases in systolic arterial pressure and systemic vascular resistance and decreases in cardiac index with cross-clamping of the distal aorta.[1,4] These changes have been ascribed to the sudden decrease in arterial vascular volume; they are most marked in patients with preexisting arterial hypertension.[5] Although the majority of the patients in this study had significant hypertension preoperatively, no patient demonstrated evidence of left ventricular failure (as measured by an increase in PCWP) or myocardial ischemia (as determined by ST-segment depression in lead V_5 of the EKG) with aortic cross-clamping. Our data do not reveal why hypertension did not occur with aortic occlusion in this study. However, one explanation could be the increase in venous capacitance and reduction in venous return to the heart which is known to occur during both epidural and morphine anesthesia.[6,7]

Hypotension following release of aortic occlusion is a more common problem during surgery on the distal aorta and/or its branches. "Declamping shock" has been described by many investigators and attributed to a multitude of changes that can take place during reduced circulation to the lower trunk and extremities.[4,8,9] The incidence of this complication is unknown, but there are a number of reports of irreversible hypotension and death following release of aortic occlusion.[4,8] In this study, severe hypotension was experienced in patients in group II and modest hypotension in patients in group IV with aortic declamping. Patients in groups I and III experienced no significant changes in $\overline{BP}$ following unclamping of the aorta. Although our findings do not elucidate the cause of declamping shock our data suggest that the lack of hypotension and stability of cardiovascular dynamics with release of aortic occlusion in groups I and III were due to increased volume replacement and increased ventricular filling pressures prior to aortic declamping.

Our data do not readily explain why decreases in $\overline{BP}$ and $\overline{PCWP}$ were more severe in group II than group IV following release of the aortic cross-clamp. Indeed, calculation of intraoperative fluid volume administered up to cross-clamp release, in milliliters per kilogram rounded to the nearest whole number, for groups I through IV are: 49, 40, 29 and 28, respectively. In spite of receiving 25% more intraoperative volume (on a weight basis) than patients in group IV, patients in group II experienced severe decreases in $\overline{BP}$ and $\overline{PCWP}$ whereas patients in group IV did not. Perhaps the explanation for these differences is that patients in group II had a greater increase in their capacitance vessel volume, secondary to the sympathetic blockade associated with epidural anethesia, than did patients in group IV. We did not measure venous capacitance; however, the significantly higher SVR of patients in group IV in comparison to those in group II throughout the study is consistent with a greater sympathetic block in the latter group. Patients in group I with the same amount of sympathetic blockade and the same increase in capacitance vessel volume as patients in group II may not have sustained significant decreases in $\overline{BP}$ and $\overline{PCWP}$ with cross-clamp release because of the additional 25% increase in intraoperative volume they received to increase $\overline{PCWP}$ above pre-anesthetic control values.

In conclusion, the results of this study demonstrate that aortic cross-clamping and release produce little change in cardiovascular dynamics in patients anesthetized with epidural or morphine-nitrous oxide anesthesia provided that left ventricular filling pressures are increased with volume loading prior to removal of the aortic clamp. In contrast, hypotension may result following release of the aortic clamp in patients in whom intravascular volume has not been increased by expanded intravenous lactated Ringer's solution prior to declamping, especially in patients given epidural anesthesia.

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Cumulative Dose-Response Curves for Gallamine: Effect of Altered Resting Thumb Tension and Mode of Stimulation

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DONLON, J. V. JR., SAVARESE, J. J., AND ALI, H. H.: Cumulative dose-response curves for gallamine: effect of altered resting thumb tension and mode of stimulation. Anesth Analg 58: 377-381, 1979.

Neuromuscular blockade studies often use the thumb adductor twitch response to ulna nerve stimulation. Two factors that may influence the results are the resting muscle tension (initial fiber length) and the pattern of the stimulus wave form. This study was undertaken to improve understanding of the effect of these factors and lead to better controlled study conditions and more consistent data. During nitrous oxide-barbiturate-narcotic anesthesia in 10 normal adult patients, as the resting thumb tension was increased from 50 to 200 g, the evoked thumb adductor twitch response (Grass stimulator, 0.25 Hz) was augmented by 28%. There was only a 2.5% increase in the evoked (developed) tension when the resting tension was further increased from 200 to 300 g. Developed tension at 50 g was significantly ($p < 0.001$) less than at the other resting tensions. The developed tension at 100 g was also significantly ($p < 0.05$) less than at resting tensions of 200 or 300 g.

Cumulative dose-response curves for gallamine in nine patients were not significantly altered by increasing resting tension from 50 to 200 g. Biphasic (Block-Aide monitor) or single square wave (Grass stimulator) stimuli wave forms in nine normal adult patients yielded gallamine dose-response curves that were not statistically different. The muscle response to biphasic stimulation during a non-depolarizing blockade was not affected by the average muscle refractory period.

Because of the significantly lower developed tension at resting tension settings of 50 to 100 g, a practical consideration during neuromuscular function studies would be to have the resting thumb tension adjusted and rechecked for each patient and kept within the 200–300-g range to ensure maximum uniform developed tension. The type of stimulus wave form selected will not affect results as long as it is used consistently throughout the study.

Key Words: NEUROMUSCULAR RELAXANTS: gallamine; NEUROMUSCULAR TRANSMISSION: nerve stimulator; MEASUREMENT TECHNIQUES: neuromuscular blockade.

MANY techniques have been used to evaluate the response to neuromuscular blocking agents in man. The most commonly used and most scientific approach is to record the evoked response of the thumb adductor muscle to ulnar nerve stimulation. Several factors may influence the accuracy of this method.

The magnitude of the evoked muscle response depends on the initial muscle fiber length, which is determined by the resting tension of the thumb.[1]

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Thus, a change in the resting tension could alter the magnitude of the evoked muscle response to ulnar nerve stimulation. It has not yet been shown whether this might also affect the overall dose-response curve for neuromuscular blocking agents in man.

The mode of ulnar nerve stimulation should also be considered when determining evoked muscle twitch responses in man. Stimulation of the ulnar nerve in clinical studies of neuromuscular blocking agents is usually done using either the Block-Aide monitor,[2] (Burroughs Wellcome Company), which delivers a biphasic spike stimulus,[3] or a Grass laboratory stimulator,[4, 5] which delivers a single square wave pulse. It has been shown that, at equal supramaximal stimulus levels, the absolute developed tension is greter with a Block-Aide stimulus than with the Grass pulse.[3, 6] Thus, the resultant neuromuscular blocking agent dose-response curve might be influenced by the nature of the ulnar nerve stimulus.

The purpose of this study was to evaluate the influence of two factors on the results of neuromuscular blockage studies. First, to measure the effect of varying the resting muscle tension (initial fiber length) on the resultant evoked (developed) twitch tension and to evaluate whether changes in resting tension after the results of dose-response curves for gallamine. Second, to investigate the significance of using either a biphasic (Block-Aide monitor) or single impulse wave form (Grass S-88 stimulator) for ulnar nerve stimulation when generating cumulative dose-response curves for gallamine. Full evaluation of the influence of resting tension and monophasic and biphasic stimulation on the dose-response to neuromuscular blocking drugs in man will help standardize study conditions and thus facilitate meaningful comparisons of data.

Methods

Adult A.S.A. class I patients scheduled for elective surgery were studied. Premedication consisted of 0.4 mg of atropine intramuscularly (IM) plus either meperidine, 0.7 mg/kg, or pentobarbital, 1.5 mg/kg, IM. Anesthesia was induced with thiopental, 3 to 5 mg/kg IV. A balanced general anesthetic technique consisting of intravenous thiopental and meperidine plus 66% nitrous oxide in oxygen administered by mask in a semiclosed system was used throughout the study period. The polygraph recorded output of a Grass FT-10 force displacement transducer was calibrated by using known weights of 50, 100, 200, and 300 g as inputs. This transducer was used to measure evoked thumb adduction in response to a single repeated supramaximal ulnar nerve stimulus. This stimulus was generated by a Grass S-88 stimulator through a stimulus isolation unit. Steel 22-gauge needle electrodes were placed subcutaneously over the ulnar nerve at the wrist. The stimulus was a single impulse of 0.2-msec duation at a rate of 0.25 Hz and a voltage 20% greater than that necessary for maximal response. In nine patients, the Grass stimulus was replaced by a Block-Aide monitor unit with fresh batteries at maximal voltage. The Block-Aide monitor wave form consists of two unequal pulses of opposite polarity separated by 5 msec.[3]

Initially, in 10 patients thumb resting tensions were adjusted to 50, 100, 200, or 300 g after general anesthesia was induced with thiopental but prior to administration of any muscle relaxants. The thumb was attached to the calibrated transducer and the degree of thumb adduction was gradually increased until the desired tension was reached as indicated by the polygraph readout. The magnitude of the supramaximal evoked thumb adductor response (developed tension) was measured and recorded. The mean developed tension ± SE was calculated for each initial load and plotted to show the relation of initial fiber length (resting tension) to developed tension.

Cumulative dose-response curve studies[5] for gallamine were carried out in three groups of nine patients each with thumb resting tension adjusted to 50, 100, or 200 g. The Grass single impulse ulnar nerve stimulus was used. The evoked thumb adductor twitch height was recorded during a control period while the patient was receiving 66% nitrous oxide and 34% oxygen by mask and had received approximately 6 mg/kg of thiopental and 1 mg/kg of meperidine, IV. Incremental intravenous doses of 0.3 to 0.5 mg/kg of gallamine were given. The evoked muscle twitch response was observed after each dose increment until a maximum effect had been reached and no greater than 2.5% change in the twitch height had occurred for a 1-minute period. This was repeated until at least three dose-response data points were measured. During this period, each patient's ventilation was controlled by hand. The data for each patient were plotted on log probit paper as a dose-response curve and effective doses for 30, 50, 80, and 95% twitch suppression were determined. Finally, mean effective doses for 30, 50, 80, and 95% twitch suppression were calculated for each resting tension group.

Additional gallamine cumulative dose-response curves were obtained in two groups of nine patients each using the above methods. The resting tension on the thumb in this portion of the study was 200 g. In one group the ulnar nerve stimulus was provided by a Block-Aide monitor unit with fresh batteries at maximal voltage, and in the other group the stimulus was a Grass S-88 stimulator impulse of 0.2-msec duration at supramaximal voltage of 0.25 Hz. The two resultant mean cumulative dose-response curves were plotted on log probit paper.

All dose-response curves were tested for parallelism and for deviation from identity using the method of Litchfield and Wilcoxon.[5]

Results

Table 1 shows mean maximal developed thumb adductor twitch tensions at various resting tensions. Developed tension was augmented as thumb resting tension was increased. As the resting tension was increased from 50 to 200 g, there was a 28% increase in developed tension. As resting tension changed from 200 to 300 g, however, there was only a 2.5% increase in developed tension. All of the developed tension values were compared with each other by paired *t*-test.[8] The twitch tension developed at 50-g resting tension was statistically significantly ($p < 0.001$) less than twitch tensions developed at 100-, 200-, or 300-g resting tension. The tension developed at 100-g resting tension was statistically significantly ($p < 0.05$) less than developed tensions at 200- or 300-g resting tension.

The effect of varying resting tension on cumulative gallamine dose-response curves is shown in Table 2. Dose-response curves measured at 50-, 100-, and 200-g resting tension were compared by the Litchfield-Wilcoxon method and did not deviate significantly from parallelism nor did they differ significantly in potency.

The effect of using either a Block-Aide monitor or Grass S-88 stimulus to determine cumulative dose-response curves for gallamine with a 200-g pre-load tension is shown in Table 3 and also as a log probit plot in the Figure. The curves generated did not differ significantly from parallelism nor from identity when tested by the Litchfield-Wilcoxon method.[7]

TABLE 1

Effect of Thumb Resting Tension on Developed Thumb Twitch Tension

Resting thumb tension	Developed twitch tension
g	*g* ± *SE*
50	312.8 ± 34.8*
100	371.3 ± 39.0†
200	399.8 ± 37.7
300	410.0 ± 35.6

* Statistically significantly different from 100-, 200-, or 300-g results by paired *t*-test ($p < 0.001$).

† Statistically significantly different from 200- and 300-g results by paired *t*-test ($p < 0.05$).

TABLE 2

Effect of Thumb Resting Tension on Cumulative Gallamine Dose-Response Curves*

Resting tension	Mean effective dose			
	Ed$_{30}$	ED$_{50}$	ED$_{80}$	ED$_{95}$
g	*mg/kg* ± *SE*			
50	0.74 ± 0.07	0.91 ± 0.09	1.23 ± 0.13	1.77 ± 0.16
100	0.79 ± 0.08	0.98 ± 0.10	1.38 ± 0.12	1.91 ± 0.14
200	0.77 ± 0.13	0.96 ± 0.14	1.36 ± 0.17	1.91 ± 0.19

* Compared by the Litchfield-Wilcoxon method,[7] the dose-response curves above were not statistically significantly different.

TABLE 3

Cumulative Dose-Response Curves for Gallamine Using Either a Block-Aide Monitor or a Grass S-88 Stimulus*

Twitch supression	Mean effective dose	
	Block-Aide	Grass
%	*mg/kg* ± *SE*	
30	0.74 ± 0.11	0.77 ± 0.13
50	0.94 ± 0.13	0.96 ± 0.14
80	1.31 ± 0.16	1.36 ± 0.17
95	1.85 ± −0.18	1.91 ± 0.19

* Compared by the Litchfield-Wilcoxon method,[7] these two dose-response curves do not differ significantly from parallelism or identity.

Discussion

The relationship between initial muscle fiber length in animals as determined by resting tension and the maximal developed tension is well known in the physiology literature.[1] There is no reason to doubt that this is not also true in man; however, this has not yet been documented quantitatively in man The results shown in Table 1, like the Starling curve for cardiac muscle, relate initial fiber length to developed force. From these results, it is clear that the thumb adductor muscle requires a 200-g pre-load to develop its maximal twitch-tension response. Therefore, it is important that the thumb resting tension should be measured and adjusted to be at least 200 g during neuromuscular studies.

In clinical studies it is common practice to measure neuromuscular blockade by referring to the evoked twitch height as a percentage of the control twitch height obtained prior to the blockade. Bearing in mind that this twitch height is in fact the developed tension,

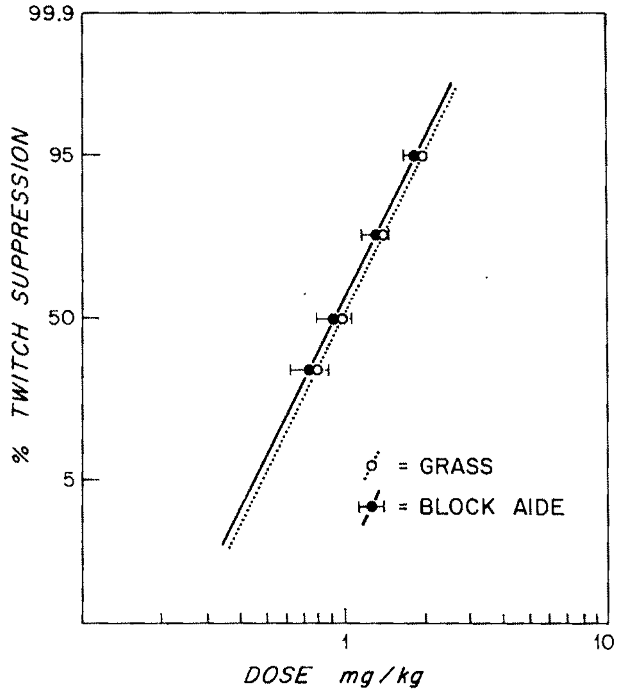

FIGURE. Cumulative dose-response curves. Log probit plot of data from Table 3. Biphasic Block-Aide stimulation compared to Grass S-88 single square wave stimulus.

then from Table 1 it is clear that if during an experiment the initial resting tension changes from 200 to 50 g due to a change in the patient's position or accidental movement then this may decrease the maximal developed twitch tension by as much as 20 to 25%. Hence, it is important to keep the resting tension constant during the study of each patient and uniform throughout the study.

As shown in Table 2, the overall cumulative dose-response curve for a neuromuscular blocking agent is not significantly affected by altering thumb resting tensions. In particular, at resting tensions of 100 and 200 g, the dose-response curves are virtually identical. The mean effective dose values obtained at 50-g resting tensions, although statistically not different, are consistently 7 to 12% less than the mean effective doses obtained at 100- and 200-g resting tension. If comparisons of potency are to be made, it is suggested that resting tension be adjusted to approximately 200 g so as to minimize the effect of spurious variations in resting tension.

Epstein and Jackson[9] have reported that the muscle twitch response to the biphasic type Block-Aide monitor stimulus may be altered as the average neuromuscular refractory period changes at increased levels of anesthesia. As shown in the Figure, the mode of stimulus, either biphasic or single impulse, did not affect the overall cumulative dose-response curve results. Epstein et al.[3] have shown that the twitch height evoked by stimulation with the Block-Aide monitor biphasic impulse is greater than that evoked by stimulation with the Grass single 0.1-msec square wave impulse. Since the degree of neuromuscular blockage is usually expressed as a percent of the control twitch height, it is important that a consistent mode of stimulus be used during clinical studies of neuromuscular blockade.

The paired impulses of the Block-Aide monitor stimulus are separated by 5 msec.[3] The average neuromuscular refractory period (ARP) is defined as the pair interval that produces muscle tension, which is the average of the tension evoked from a single stimulus and the maximum tension evoked by a paired stimulus.[10] Since the average neuromuscular refractory period is 1.77 msec during light anesthesia with halothane, ether, methoxyfluorene, or fluoroxene, and increases to an average of 2.33 msec with deeper anesthesia,[9] it would seem that the biphasic nature of the Block-Aide monitor would not be a factor influencing the muscle twitch response. Increasing degrees of nondepolarizing neuromuscular blockage have been shown to lower the ARP.[11] As shown in the Figure, the use of a biphasic type of stimulus of 5-msec separation does not affect the twitch response results. The muscle should always respond to both impulses of the paired stimulus.

The conditions and methods of stimulation and measurement during evaluation of the effect of neuromuscular blocking agents in man must be standardized to achieve uniform results and to permit meaningful comparisons of data reported in the literature.

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Nitrogen-Sparing Intravenous Fluid Therapy

The postoperative protein-sparing effect of intravenously administered amino acids was assessed quantitatively by measuring body composition by multiple isotope dilution. Body composition was determined in two groups of 19 patients each, before and on the 5th day following a major abdominal operation. One group of patients received all of their required fluids and electrolytes as a 5% glucose solution. The second group received an isocaloric infusion of protein as a 5% casein hydrolysate solution. The preoperative body composition of both groups was normal. On the 5th day after operation, the mean body weight had decreased by 2.6 ± 0.6 kg in the glucose group and by 2.0 ± 0.5 kg in the protein group. In the patients receiving glucose, this postoperative weight loss was due to a decrease in both body fat and the mean body mass. The mean body cell mass, which represents the total mass of living, functioning cells, decreased from 23.1 ± 1.5 to 19.9 ± 1.4 kg ($p < 0.001$), while the extracellular mass increased from 24.9 ± 0.9 to 27.3 ± 0.9 kg ($p < 0.001$). In contrast, in the patients receiving protein, the loss of body weight resulted entirely from a loss of body fat, while the body cell mass and the extracellular mass both remained normal. The data demonstrate that protein sparing was achieved by the postoperative infusion of protein. (*Shizgal HM, Milne CA, Spanier AH: The effect of nitrogen-sparing, intravenously administered fluids on postoperative body composition. Surgery 85:496–503, 1979*)

Barbiturates and Hypothermia in Brain Edema

The effect of pentobarbital and hypothermia on the development of ischemic brain edema was studied in 23 rhesus monkeys undergoing transorbital middle cerebral artery occlusion. Fifteen additional animals served as unclipped controls. Regional cortical cerebral blood flow (rCBF), arteriovenous oxygen content difference ($AVDO_2$), and regional cortical metabolic rate of O_2($rCMRO_2$) were measured hourly until sacrifice 11 hours postocclusion, at which time ischemic cerebral edema was measured. In eight animals no treatment followed the occlusion, and these developed significant edema. In seven animals pentobarbital, 14 mg/kg, was administered intravenously 30 minutes after occlusion and 7 mg/kg every 2 hours thereafter. In this group ischemic brain edema was negligible. In eight animals, hypothermia to 25.9 ± 0.5 C was started 30 minutes after occlusion and maintained until sacrifice; ischemic brain edema was not significantly altered from untreated-clipped animals. On the basis that both pentobarbital and hypothermia produced similar changes in rCBF, $AVDO_2$, and $rCMRO_2$, but only pentobarbital prevented edema, it is postulated that the mode of action of barbiturates in preventing ischemic brain edema is not entirely related to their known effect on blood flow and metabolism. (*Simeone FA, Frazer G, Lawner P: Ischemic brain edema: comparative effects of barbiturates and hypothermia. Stroke 10:8–12, 1979*)

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Pharmacokinetics of Intravenous Procaine Infusion in Humans

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SEIFEN, A. B., FERRARI, A. A., SEIFEN, E. E., THOMPSON, D. S., AND CHAPMAN, J.: Pharmacokinetics of intravenous procaine infusion in humans. Anesth Analg 58:382-386, 1979.

Pharmacokinetic data during and following the continuous intravenous infusion of procaine are lacking. We studied 12 women undergoing hysterectomy during N_2O-O_2 and narcotic anesthesia. A constant infusion of 2% procaine was administered at a rate of 1 mg/kg/min to six patients (group I) and at a rate of 1.5 mg/kg/min to the other six (group II). Procaine plasma levels were determined by flame ionization gas-liquid chromatography. Using a two-compartment pharmacokinetic model, disposition kinetics were studied. Steady-state plasma levels were achieved within 20 to 30 minutes after commencement of the infusion. Following termination of the infusion the drug disappeared with a distribution half-life ($t\frac{1}{2}\ \alpha$) of 2.49 ± 0.36 minutes and an elimination half-life ($t\frac{1}{2}\ \beta$) of 7.69 ± 0.99 minutes at both infusion rates. In group I, the fraction of drug in the central compartment was 65%, the volume of distribution at steady-state was 0.79 ± 0.14 L/kg, and total body clearance 0.08 ± 0.01 L/kg/min. In group II, the fraction of drug in the central compartment was 82%, the volume of distribution at steady-state 0.34 ± 0.07 L/kg, and the total body clearance 0.04 ± 0.01 L/kg/min. These data indicate that procaine is a drug of limited distribution and tissue uptake with a short duration of action.

Key Words: ANESTHETICS, Local: procaine; PHARMACOKINETICS: intravenous procaine.

PROCAINE hydrochloride is commonly used as a local anesthetic. It also has pharmacologic actions that can be used effectively during general anesthesia including suppression of cardiac arrhythmias,[1,2] respiratory tract reflexes, and secretions.[3,4] Procaine also possesses weak analgesic,[5,6] and muscle relaxing properties.[4] Procaine has a short duration of action due to its rapid hydrolysis by pseudocholinesterases to relatively inactive metabolites, para-aminobenzoic acid and diethylaminoethanol.[7,8] We measured plasma procaine levels and calculated pharmacokinetic data in patients to whom procaine was administered by continuous intravenous infusion during surgical anesthesia. Such data have not been previously reported.

Methods and Materials

Twelve adult female patients of A.S.A. status 1 or 2 scheduled for surgical procedures of the lower abdomen (total vaginal or total abdominal hysterectomy) were selected. Patients were excluded from the study when the preoperative evaluation revealed any systemic disease such as diabetes, hypertension, seizure disorder, or cardiovascular or renal disease. Each patient signed a written, informed consent and the study was approved by the local Committee on Human Research.

Patients were divided into two groups, each consisting of six patients: group I received 1 mg/kg/min of procaine for 60 minutes and group II 1.5 mg/kg/

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min for 60 minutes. The selection of these doses was based upon the work of Usubiaga and Wikinski[9] and on the observation that in dogs 1 to 2 mg/kg/min of procaine in combination with the administration of 50% N_2O produces analgesia.[6]

In order to avoid prolonged action of procaine, dibucaine numbers were determined prior to administration of anesthesia to exclude patients with atypical plasma cholinesterases.[10] A simple screening test (Acholest, Fougera, Hicksville, NY) was used to assess plasma cholinesterase activity.

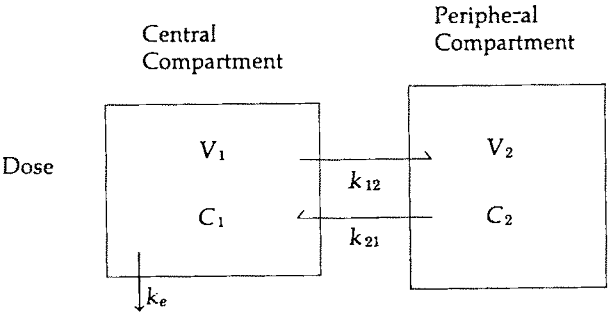
All patients received morphine sulfate, 0.1 mg/kg, and atropine, 0.4 mg IM, as premedication approximately 1 hour before induction of anesthesia. A radial artery and a peripheral vein were catheterized percutaneously. Anesthesia was induced with thiamylal, 3 to 4 mg/kg IV, after preoxygenation with 100% O_2 for 3 to 5 minutes. Endotracheal intubation was facilitated by intravenous administration of succinylcholine, 1 mg/kg. Following endotracheal intubation a 2% procaine hydrochloride solution in 5% dextrose in water was administered as continuous infusion with a calibrated Harvard pump. Dose calculations were based on lean body mass (Weisberg's modification of Gubner's formula)[11] rather than total body weight. All patients were artifically ventilated with 50% N_2O and O_2. Arterial blood gases were analyzed prior to induction of anesthesia and every 30 minutes throughout the operation. Blood pressure and electrocardiogram (lead II) were continuously monitored using a Hewlett-Packard multichannel-recorder (model no 7754 N) and pharyngeal temperature was determined using a Yellow-Springs thermistor.

Intraoperative intravenous fluid administration ranged from 600 to 1100 ml of 5% dextrose in Ringer's lactate solution at the rate of 5 ml/kg/hr. Whole blood was administrated if blood loss exceeded 15% of the patient's calculated total blood volume.

Plasma concentrations of procaine were measured before induction and 1, 3, 5, 10, 15, and 20 minutes[4] following initiation of the constant infusion. Thereafter, procaine levels were measured every 20 minutes. The infusion was maintained for 60 minutes. After discontinuation procaine plasma levels were measured at 1, 3, 5, 10, 15, 20, and 40 minutes. Blood samples for measurement of procaine levels were drawn from the indwelling arterial catheter into 5-ml Vacutainer tubes containing sodium heparin plus 5 mg of echothiopate. Addition of echothiopate, 1 mg, to 1 ml of plasma ensured 100% recovery of procaine from blood samples.[12] Blood samples were centrifuged for 20 minutes at 5000 rpm and the plasma analyzed. Analysis of procaine plasma concentrations was made by flame-ionization gas-liquid chromatography.[12] Detection limit of this method in our laboratory was 0.1 μg/ml.

Procaine infusion was limited to 60 minutes to enable comparison of the rate of decline of plasma levels. (If necessary, anesthesia was continued with enflurane, 1 to 2%, and 50% N_2O and O_2).

Plasma level data were fitted into a two-compartment open pharmacokinetic model with first order drug elimination:[13]



where C_1 and C_2 represent drug concentration in V_1 and V_2, volumes of the central and the peripheral compartments, respectively; k_{12} and k_{21} are first order rate constants of drug transfer between peripheral and central compartment; and k_e is the first order rate constant for drug elimination from the central compartment. Half-lives of the disappearance phases ($t\frac{1}{2}\ \alpha$, $t\frac{1}{2}\ \beta$), total apparent volume of distribution at "steady-state" (V_Dss), total plasma clearance (Cl_p), the first order rate constants for drug transfer between the two compartments (k_{12}, k_{21}) and the elimination rate constant (k_e) were calculated from the "hybrid coefficients" (A, B, α, β) as described by Greenblatt and Koch-Weser.[13, 14]

The "hybrid coefficients" α, β, A, and B were derived from ln of procaine plasma levels versus time after termination of the infusion. α and β represent the slopes for distribution and elimination, respectively. $A + B$ is the intercept with the ordinate at time 0 of the distribution curve (slope α); B represents the intercept with the ordinate at time 0 of the elimination curve (slope β).

The fraction of drug in the central compartment (f_c) was calculated from the following formula: $f_c = \beta / k_e$ where β = slope of elimination and k_e = elimination constant.

Kinetic indices were derived by least squares analysis of log concentrations (μg/ml) versus time relationships.

The data were analyzed by Student's t-test and are presented as means ± standard error of the mean (SEM) with $p < 0.05$ as the minimal acceptable level of significance.

Results

Patient data are shown in Table 1. There was little variation in the average age and weight. However, two patients in group II were significantly obese; thus the total procaine dose calculated for lean body mass did not increase linearly with total body weight. Mean plasma procaine levels are plotted in Fig 1. Steady-state levels were achieved within 20 to 30 minutes after commencement of the continuous infusion in both groups of patients: in group I the mean steady-state level was 12.7 ± 1.2 µg/ml in group II, 42.7 ± 7.1 µg/ml.

After termination of the infusion the drug disappeared with an initial half-life $t\frac{1}{2}\ \alpha$ (distribution) of 2.49 ± 0.36 minutes and an elimination half-life $t\frac{1}{2}\ \beta$ of 7.69 ± 0.99 minutes (Fig 2).

Forty minutes after discontinuing the procaine infusion, 96 to 98% of the drug was eliminated.

The data from each patient were fitted to a two-compartment open pharmacokinetic model with first order drug elimination. The kinetic parameters are shown in Table 2.

With the use of the "hybrid coefficients" the following parameters were calculated: in group I the apparent volume of distribution at steady-state $V_{D}ss$ was 58.68 ± 4.08 L or 0.79 ± 0.14 L/kg and total body clearance Cl_p 6.23 ± 0.78 L/min or 0.08 ± 0.01 L/kg/min.

In group II $V_{D}ss$ was 23.55 ± 3.90 L or 0.34 ± 0.07 L/kg and Cl_p was 2.42 ± 0.39 L/min or 0.04 ± 0.01 L/kg/min.

The fraction of drug in the central compartment $f_c = \beta/k_e$ was 65% in group I and 82% in group II.

Mean arterial pressure (MAP) rose 15 torr (mean) in group I, which was not statistically significant, and did not change in group II. Heart rate (HR) increased by 10 beats/min (mean) above control in group I and did not change in group II. The increases in MAP and HR in group I, although not statistically significant, indicate less adequate analgesia with the lower dose. Arterial blood gases were compared at three time

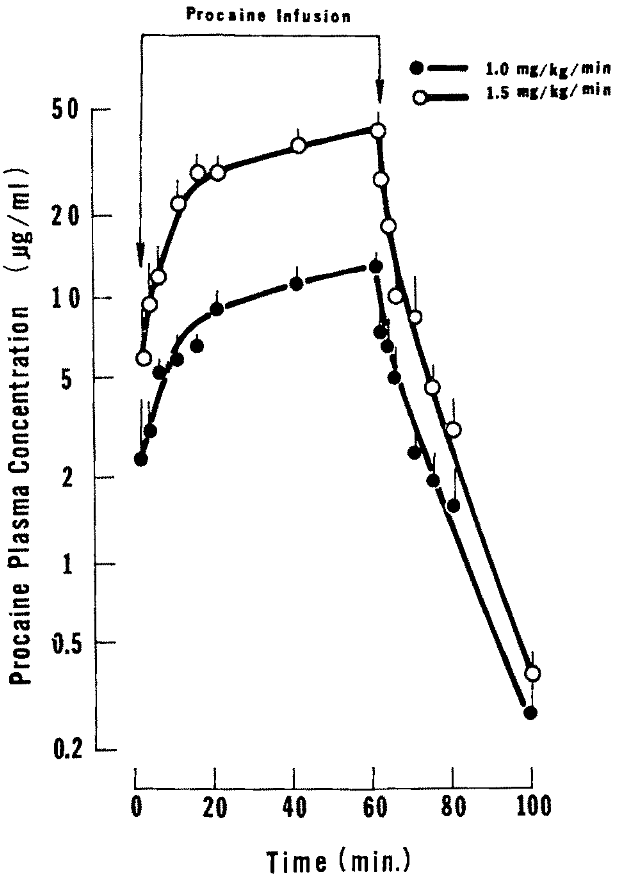


FIG 1. Plasma concentrations of procaine hydrochloride in six patients during and following 60 minutes of infusion at rates of 1 mg/kg/min or 1.5 mg/kg/min (mean ± SEM).

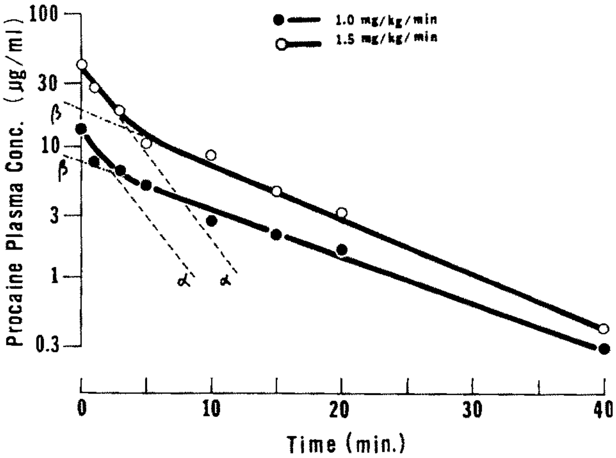


FIG 2. Plasma log concentration versus time relationship after a 60-minute constant infusion of procaine at two infusion rates. "Hybrid coefficients" were determined from these curves (see text).

TABLE 1

Patient Data

Group (n = 6)	Age	Weight	Total procaine dose*
	yr	*kg*	*g*
I (1 mg/kg/min)	40 ± 5.7	82 ± 10.0	4.3 ± 0.5
II (1.5 mg/kg/min)	35 ± 3.5	74 ± 12.6	4.9 ± 0.6

* Dose calculations are based on lean body mass rather than total body weight.

TABLE 2

Pharmacokinetic Parameters for Procaine Hydrochloride Infusion (mean ± SEM)*

	Group I (n = 6) (1 mg/kg/min)	Group II (n = 6) (1.5 mg/kg/min)
$A + B$	2.50 ± 0.11	3.66 ± 0.78
B	1.72 ± 0.33	2.78 ± 0.29
A	0.79 ± 0.25	0.88 ± 0.20
α	0.326 ± 0.064	0.406 ± 0.127
β	0.094 ± 0.030	0.100 ± 0.007
k_e min^{-1}	0.144 ± 0.038	0.122 ± 0.009
k_{12} min^{-1}	0.046 ± 0.018	0.058 ± 0.029
k_{21} min^{-1}	0.230 ± 0.052	0.326 ± 0.097
t½ α min	2.71 ± 0.63	2.27 ± 0.39
t½ β min	8.30 ± 1.30	7.09 ± 0.53
V L/kg	0.67 ± 0.13	0.30 ± 0.15
$V_D ss$ L/kg	0.79 ± 0.14	0.34 ± 0.07
Cl_p L/kg/min	0.08 ± 0.01	0.04 ± 0.01

* See text for definition of abbreviations.

periods: preoperative, during spontaneous ventilation of room air; intraoperative, during controlled ventilation with 50% O_2; and postoperative, during spontaneous ventilation of 40% O_2 via face mask. Pa_{O_2} values correlated well with inspired O_2 concentration, indicating that the ventilation-perfusion ratio was not altered. Pa_{CO_2} remained normal during the two periods of spontaneous ventilation (38 to 41 torr).

Moderate hyperventilation was used intraoperatively (Pa_{CO_2} = 35 torr). Base excess (−2.5 to 3.0) indicated slight metabolic acidosis during procaine administration and in the immediate postoperative period.

Discussion

Procaine has certain useful pharmacologic properties which could be successfully employed during general anesthesia. These include an antiarrhythmic action;[1, 2] an anticholinergic effect causing suppression of reflexes and of secretions of the respiratory trace;[4, 17] neuromuscular blocking capability; analgesia; and inhibition of baroreceptor reflexes.[18]

These properties can provide a smoother course of anesthesia for thoracotomies, laryngeal operations, neck dissections, and surgery in patients with preexisting ventricular dysrhythmias. The short duration of action makes continuous infusion mandatory. This may produce toxic effects due to high plasma levels, as manifested by hypotension and convulsions. Therefore it was essential to determine infusion rates which produce safe steady-state levels below the toxic range.

Usubiaga et al[19] reported that convulsions occur with plasma concentrations ranging from 20–80 μg/ml. In their study unpremedicated volunteers received procaine infusions at rates of 3 to 9 mg/kg/min while breathing spontaneously, plasma levels were determined in venous samples, and a different analytic technique was used for plasma procaine levels. Comparison with our data is, therefore, difficult. Our patients in group II showed plasma levels ranging from 22.4–62.8 μg/ml. No toxic central nervous system effects such as mydriasis, muscle tremors, or convulsions were observed. However, these patients received thiamylal and diazepam during induction of anesthesia, drugs known to increase local anesthetic convulsive thresholds.[20]

The pharmacokinetics of distribution and elimination of procaine hydrochloride during and after 60 minutes of intravenous infusion at two infusion rates, 1 mg/kg/min and 1.5 mg/kg/min, were assessed. Steady-state levels were approached within 20 to 30 minutes. The relationship between infusion rates and steady-state levels was not linear: there was a 350% increase in procaine plasma levels with a 50% increase of infusion rate. This indicates saturation of some disposition process. Inhibition of the enzyme pseudocholinesterase which hydrolyses procaine did not occur at the infusion rates used since the elimination half-life remained the same at both rates. There are data showing that enzyme inhibition may occur when procaine is infused at rates of 10 mg/kg/min or greater.[21]

The calculated total apparent volume of distribution was 2.5 times greater with the infusion rate of 1 mg/kg/min than with 1.5 mg/kg/min, indicating a low drug concentration in the tissue. The fraction of drug in the central compartment (f_c), which is primarily the vascular space, was 65% in group I and 82% in group II. The low lipid solubility of procaine is likely to account for its minimal distribution and tissue uptake as compared to other local anesthetics.[22] Limited tissue uptake might explain the nonlinear increase in plasma levels with dose increase.

In conclusion, the kinetic profile of procaine during and after a continuous infusion at two different rates indicates that a steady-state is reached within 20 to 30 minutes. The elimination half-life t½ β was found to be 7.69 minutes. No enzyme inhibition was observed. Steady-state plasma levels did not increase linearly with an increase in infusion rate. Procaine is a short-acting drug with a brief half-life and a limited degree of distribution and tissue uptake.

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Physostigmine in Drug Overdose

Twelve patients with coma due to drug overdose were treated with physostigmine salicylate in a double-blind, placebo-controlled crossover trial. Three of the nine patients who had taken drugs without anticholinergic action (methyprylon, barbiturates, ethchlorvynol, benzodiazepines) and two of three who had taken drugs with anticholinergic action (amitriptyline) showed dramatic decrease of depth of coma after physostigmine. Among patients with non-anticholinergic overdose, in 10 minutes, physostigmine induced significant increases in mean arterial pressure from 80.3 mm Hg (mean) to 103.8 mm Hg and in heart rate from 87.9 beats/min to 98.3 beats/min. When given to patients with anticholinergic drug intoxication, physostigmine induced a significant fall in mean arterial pressure from 105.4 mm Hg to 96.1 mm Hg and in heart rate from 104 beats/min to 91.3 beats/min. Physostigmine induced dilation of pupils in all patients with non-anticholinergic overdose and in none with anticholinergic overdose. The effects of physostigmine in non-anticholinergic overdose appear to be due to a nonspecific action on the central nervous system. Physostigmine may also be of value in the differential diagnosis of coma. Its routine use in the treatment of drug-induced coma is not recommended except in anticholinergic drug overdose unless standard measures fail and artificial mechanical ventilation cannot be provided to patients with severe drug-induced respiratory depression. (*Nattel S, Bayne L, Ruedy J: Physostigmine in coma due to drug overdose. Clin Pharmacol Ther 25:96–102, 1979*)

ANESTH ANALG
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Depression of Lung Mucociliary Clearance by Thiopental and Halothane

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FORBES, A. R., AND GAMSU, G.: Depression of lung mucociliary clearance by thiopental and halothane. Anesth Analg 58:387–389, 1979.

It has previously been demonstrated that an induction dose of thiopental, 25 mg/kg, without continuing anesthesia did not depress peripheral lung mucociliary clearance in the dog, whereas 2 hours of anesthesia with halothane, 1.2 MAC, did depress clearance. To determine whether this was because thiopental depresses the mucociliary apparatus less than halothane, this study compared mucociliary clearance after 2 hours of anesthesia with halothane with clearance after 2 hours of anesthesia with thiopental, 40 mg/kg. With thiopental, 40 mg/kg, 50% mucociliary clearance of tantalum from peripheral airways required 280 ± 65 (SEM) minutes, which was comparable to clearance obtained with halothane, 1.2 MAC, 382 ± 27 (SEM) minutes. Hence, thiopental depresses mucociliary clearance as much as halothane does when both are administered in equivalent anesthetic doses for equal periods of time.

Key Words: LUNG: bronchus; ANESTHETICS, Volatile: halothane; ANESTHETICS, Intravenous: thiopental.

REPORTS on the influence of barbiturates on the mucociliary apparatus are conflicting. Pentobarbital or thiamylal anesthesia depresses mucous flow in the trachea.[1] With different techniques, increasing depth of barbiturate anesthesia has been reported to stop mucous flow in the nose,[2] but not to change flow in the trachea.[3] We previously found[4] that an induction dose of thiopental, 25 mg/kg, in dogs does not depress lung mucociliary clearance. In contrast, administration of halothane or ether for 2 hours significantly prolongs mucociliary clearance.[4] The discrepancy could be due to the fact that thiopental has less depressant effect on the mucociliary apparatus than halothane or ether, or to the fact that smaller doses and shorter duration of anesthesia were studied with thiopental. To resolve this issue, we compared the rate of mucociliary clearance after 2 hours of halothane anesthesia with that observed after 2 hours of thiopental anesthesia at an equivalent dose.

Methods

Lung mucociliary clearance during anesthesia was examined by tantalum bronchography[5] in six healthy hounds with previously documented good mucociliary flow[4] during (1) thiopental administration for 2 hours (40 mg/kg total) with controlled ventilation and endotracheal intubation using a tidal volume of 30 ml/kg; and (2) during halothane administration at 1.2 MAC for 2 hours with controlled ventilation and endotracheal intubation with tidal volumes of 30 ml/kg. The 40-mg/kg dose of thiopental was given as an induction bolus of 25 mg/kg, followed by three doses of 5 mg/kg at ½-hour intervals. The dosage schedule

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for thiopental was selected on the basis of the following observations:

In two dogs, after induction of anesthesia with thiopental, 25 mg/kg, the tail was clamped each 5 minutes until limb movement resulted. When movement resulted, thiopental, 5 mg/kg, was given and tail clamping resumed until movement again resulted. This sequence was repeated and the intervals between movements were noted to be 35 to 40 minutes. On subsequent occasions when the 5-mg/kg dose was given at 30-minute intervals, no response to clamping resulted. That the latter dose and sequence prevented movement was confirmed in all six dogs. We feel that this corresponds roughly to 1.2 MAC, which will prevent movement in response to painful stimulus in 95% of subjects.[6]

The studies, done over a 15-month period, were always in the sequence indicated above. Studies in individual dogs were separated by at least 8 months so that all studies were performed at the same time of year. In each group tantalum was insufflated endotracheally after induction of anesthesia. Inspired gas consisted of compressed air humidified to more than 90% relative humidity at 32-35 C. The endotracheal tube cuff was deflated until a leak was heard on inspiration. Inspired tidal volume was then adjusted until measured expired tidal volume was 30 ml/kg. Respiratory rate was set to maintain venous carbon dioxide tension at 30 to 40 torr. Inspiratory pressures ranged from 12-20 cm H_2O, and respiratory rates from 6-12 [per minute.]

For tantalum insufflation, a radiopaque catheter 2 mm in diameter was passed into the origin of each mainstem bronchus, and tantalum powder of mass median diameter 2.5 μ insufflated from a DeVilbiss powder blower until airways 2 to 5 mm in diameter were outlined on fluoroscopy. The trachea was then outlined as the catheter was withdrawn. Approximately 1 ml or 16 g of powder was insufflated in each dog. With the animal prone, a posteroanterior chest roentgenogram was taken after tantalum insufflation. The roentgenogram was repeated hourly using the same exposure at end inspiration while the animal lay prone in a plastic foam cradle during anesthesia. After 2 hours of anesthesia, the endotracheal tube was removed and roentgenograms repeated hourly for 6 hours.

Roentgenograms were assessed by two observers independently as follows. Each observer, unaware of the timing or sequence of films, ranked them according to the amount of tantalum remaining. Then, by comparison with standard bronchograms and referring to the radiopacity of tantalum on the initial film as 100% tantalum dose, the observer independently scored each film as percentage of tantalum remaining in peripheral airways. Percentage of tantalum cleared was assessed in 10% increments. Peripheral airways were defined as those beyond the origins of the upper lobe bronchi. Times to 50% peripheral clearance were compared by paired Student's *t*-test; *p* values less than 0.05 were considered significant.

Results

The independent film assessments by each observer gave consistent results. When the value for each film given by one author was plotted against the value of the other, a linear regression of $y = .99 \pm .08\,x$ ($r^2 = .95$) was obtained. Thiopental, 40 mg/kg, and halothane, 1.2 MAC, over 2 hours depressed peripheral mucociliary clearance to the same degree (Figure and Table). Mean time to 50% clearance of tantalum from peripheral airways was 382 ± 27 (SEM) minutes after halothane administration, and 280 ± 65 (SEM) minutes after thiopental, 40 mg/kg. The wide variability in mucociliary clearance times from dog to dog is comparable to that previously reported by us with other anesthetics and techniques.[4]

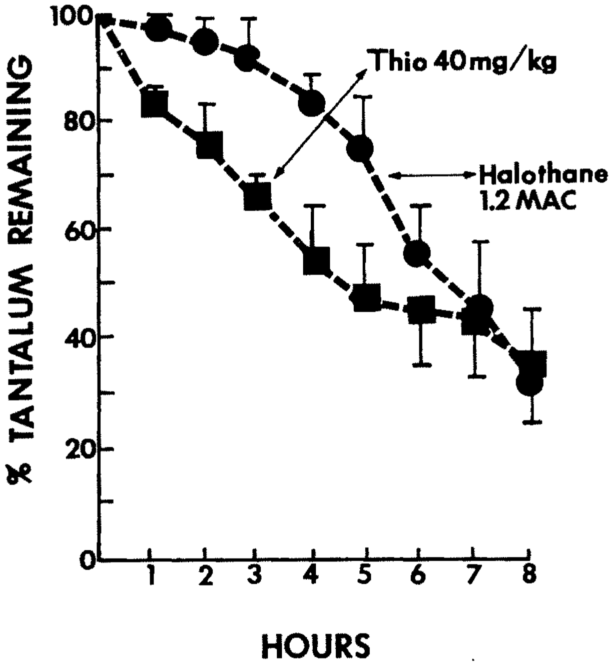

FIGURE. Rate of peripheral mucociliary clearance in six dogs anesthetized for 2 hours with halothane, 1.2 MAC, is comparable to that in the same dogs anesthetized with thiopental, 40 mg/kg.

TABLE
Time (min) to 50% Clearance of Tantalum from Peripheral Airways*

Thiopental (40 mg/kg)	Halothane (1.2 mAC)
480	440
120	320
180	380
240	360
480	480
180	312
280	382
160	66.7
65.1	27.2

* Minutes taken to achieve 50% mucociliary clearance from peripheral airways of six dogs anesthetized for 2 hours with thiopental or halothane. There is no significant difference between the rates of clearance.

Discussion

This study compares the effects of 2 hours of halothane and thiopental anesthetic on the rate of peripheral lung mucociliary clearance in dogs anesthetized under similar conditions, i.e., endotracheal intubation and mechanical ventilation. The inspired gas was humidified and the endotracheal cuff deflated to avoid depressing mucous flow. The tidal volume was chosen so that mechanical inflation and deflation of the lungs mimicked respiratory rates and airway pressures commonly used in anesthetized man. This required a volume of 30 ml/kg because the dog's lung volume is approximately 1.6 times greater per kilogram than that of man.[7]

We have demonstrated that in an equivalent dose for the same duration, thiopental anesthesia depresses lung mucociliary clearance to the same degree as does halothane anesthesia. This finding, in conjunction with previous work on mucociliary flow in the trachea and on mucociliary clearance from peripheral airways indicates that it is the state of anesthesia itself, rather than specific properties of individual anesthetics, that depresses the mucociliary apparatus. Thus, equivalent doses of halothane, enflurane, nitrous oxide with halothane, and nitrous oxide with morphine depress tracheal mucous flow equally,[8] and equivalent doses of halothane, ether,[4] and thiopental depress peripheral lung mucociliary clearance equally. Furthermore, this depression is dose dependent.[8, 9] Both these factors correlate with the dose-dependent depression of ciliary beat seen in Protozoa with a variety of anesthetics.[10]

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ANESTH ANALG
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High Dose Fentanyl Anesthesia for Coronary Artery Surgery: Plasma Fentanyl Concentrations and Influence of Nitrous Oxide on Cardiovascular Responses

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LUNN, J. K., STANLEY, T. H., EISELE, J., WEBSTER, L., AND WOODWARD, A.: High dose fentanyl anesthesia for coronary surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 58:390–395, 1979.

Plasma concentrations of fentanyl achieved during high dose fentanyl (25 to 75 μg/kg)-oxygen anesthesia were measured during and after fentanyl infusion and during and after cardiopulmonary bypass in patients with coronary artery disease. In addition, the cardiovascular effects of addition of nitrous oxide during fentanyl-oxygen were evaluated at two different plasma concentrations of fentanyl. Intravenous fentanyl (18 ± 4 μg/kg) produced unconsciousness and resulted in a mean plasma fentanyl concentration of 34 ± 7 ng/ml. Plasma fentanyl increased to 48 ± 8 ng/ml after 25 μg/kg, remained relatively constant for the remainder of the fentanyl infusion, and decreased slowly after termination of infusion. Plasma fentanyl was further decreased (to approximately 40% of peak values) with initiation of cardiopulmonary bypass but underwent little further change throughout the remainder of bypass or for 1 hour after bypass. Fentanyl (25 μg/kg) produced small decreases in mean arterial, pulmonary artery, and pulmonary capillary wedge pressures, and systemic and pulmonary vascular resistances. Additional fentanyl produced no further change in these variables. Fentanyl did not significantly change heart rate, cardiac output, or right atrial pressure at any time during the study. Addition of nitrous oxide to the inspired mixture of gases produced significant but similar decreases in cardiac output and increases in heart rate and pulmonary and systemic vascular resistances both before operation and after bypass. These data indicate that anesthetic doses of fentanyl result in plasma fentanyl concentrations that decay more slowly than analgesic doses of the compound. In addition, they demonstrate that while high dose fentanyl-oxygen anesthesia does not appreciably alter cardiovascular dynamics, addition of nitrous oxide results in significant cardiovascular depression which is similar with both high (before operation) and low (after bypass) plasma concentrations of fentanyl.

Key Words: ANALGESICS: fentanyl; ANESTHETICS, Volatile: nitrous oxide; ANESTHESIA, cardiovascular.

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HIGH DOSE fentanyl-oxygen anesthesia (50 to 100 μg/kg) produces little change in cardiovascular dynamics and has been suggested as an alternative to morphine in patients with little cardiac reserve.[1] Plasma concentrations of fentanyl achieved with this technique and the influence of cardiopulmonary bypass on these concentrations are unknown. The cardiovascular effects of nitrous oxide during high dose fentanyl anesthesia are also unknown. Since nitrous oxide can result in severe cardiovascular depression when added during narcotic-oxygen anesthesia[2-4] and the plasma concentration of the narcotic might influence this depression, we have investigated the plasma concentrations of fentanyl achieved with high dose fentanyl-oxygen anesthesia and the influence of nitrous oxide on cardiovascular dynamics at two different fentanyl plasma concentrations.

Methods

Eighteen patients about to undergo two-vessel coronary artery bypass operations were studied. Two of the patients were taking propranolol (50 to 100 mg daily); twelve patients took nitroglycerin on occasion for angina. Written informed consent was obtained from each of the patients at the time of the preoperative visit. All patients were premedicated with diazepam, 10 mg orally, and morphine sulfate, 0.1 mg/kg, and scopolamine, 0.5 mg, intramuscularly 90 minutes prior to the scheduled time of operation. Upon arrival in the induction room, catheters were placed in a hand vein and the radial artery. Prior to induction of anesthesia, a thermodilution flow-directed balloon-tipped pulmonary artery catheter (Edwards quadruple lumen thermodilution model no 93A131-7F) was percutaneously introduced into the pulmonary artery (PA) through the right internal jugular vein using a Cordis introducer.

After a 15-min period of breathing 100% oxygen, anesthesia was induced with intravenous fentanyl administered at a rate of 300 μg/min. Respirations were first assisted and then controlled at 10 to 15 breaths/min using a face mask and a semi-closed circle system to maintain Pa_{CO_2} at 35 to 40 torr as measured in radial arterial blood every 15 minutes. During infusion of fentanyl, patients were commanded to open their eyes and take a deep breath every 30 seconds. Failure to respond to three consecutive commands was equated with unconsciousness. After 50 μg/kg of fentanyl had been administered, the patients were paralyzed with intravenous succinylcholine (2 mg/kg), and the trachea was intubated with a cuffed Murphy endotracheal tube. After intubation, additional fentanyl was administered until each patient had received 75 μg/kg. Then the inspired mixture of gases was changed to 60% helium in oxygen. Fifteen minutes later the inspired mixture of gases was changed to 60% nitrous oxide in oxygen.¶ The surgical procedure began 30 minutes after nitrous oxide was started. Following skin incision, the patients were paralyzed with pancuronium (6 mg slowly intravenously). Paralysis was maintained with 1- to 3-mg increments of pancuronium every 45 to 60 minutes during cardiopulmonary bypass and in the post-bypass period. Nitrous oxide was continued until bypass. Patients breathed 100% oxygen after bypass. Forty-five minutes after bypass, when cardiovascular dynamics had stabilized, the inspired gases were changed to nitrous oxide (60% in oxygen).

Ringer's lactate solution in dextrose, 5% in water, was administered at a rate of 200 to 250 ml/hr during the entire operation. The extracorporeal system (Bentley bubble oxygenator; Sarns roller pump) was primed with 20 to 25 ml/kg of Ringer's lactate solution. Bypass flow rates were maintained at 60 to 80 ml/kg/min to keep mixed venous P_{O_2} between 37 to 43 torr (corrected for temperature changes). Patients were cooled to 32 C during extracorporeal support and rewarmed to 37 C at its conclusion. No patient required or was given positive or negative inotropic compounds during the study.

Cardiovascular dynamics measured during this investigation included heart rate ((HR) beats/min), cardiac output ((CO) L/min), and mean arterial (($\overline{BP}$) torr), mean pulmonary artery (($\overline{PAP}$) torr), mean pulmonary capillary wedge ((PCWP) torr), and mean right atrial (($\overline{RAP}$) torr) pressures. Systemic vascular (SVR) and pulmonary vascular (PVR) resistances (dynes·sec/cm^5) were calculated using standard formulas:

$$SVR = \frac{\overline{BP} - \overline{RAP}}{CO} \times 80$$

$$PVR = \frac{\overline{PAP} - \overline{PCWP}}{CO} \times 80$$

Cardiac output was measured by the thermodilution technique using the balloon-tipped flow-directed thermodilution PA catheter. Plasma fentanyl concentrations were determined by the method of Schleimer et al.[5]

¶ In six patients the sequence of addition of helium and nitrous oxide was reversed (60% nitrous oxide followed by 60% helium). Since the sequence of helium and nitrous oxide addition did not appear to influence the results, addition of the gases was not randomized throughout the remainder of the study, and values obtained with nitrous oxide and helium were combined for statistical analysis irrespective of the sequence in which they were given.

Cardiovascular dynamics were recorded immediately before anesthetic induction, after 25, 50 (following intubation), and 75 μg/kg of fentanyl (during pure oxygen breathing); 15 minutes after the inspired mixture of gases was changed to 60% helium in oxygen; 15 minutes after substitution of 60% nitrous oxide for helium; following skin incision; immediately before cardiopulmonary bypass, 45 minutes after bypass (while breathing pure oxygen); and 60 minutes after bypass (following 15 minutes of breathing 60% nitrous oxide in oxygen). Peripheral venous blood samples (10 ml) for fentanyl assay were obtained at the same time cardiovascular dynamics were recorded and at the point of unconsciousness, 15 and 60 minutes following initiation of bypass, at the termination of bypass, and 45 and 60 minutes after bypass.

Data were analyzed for statistical significance utilizing Student's paired *t*-test.

Results

The duration of bypass (90 ± 6 minutes), the duration of the entire study period (259 ± 11 minutes), and the intervals at which cardiovascular dynamics were recorded and blood samples obtained were remarkably constant in all patients. Fentanyl (18 ± 4 μg/kg, range 13–22 μg/kg) produced unconsciousness and resulted in a mean plasma fentanyl concentration of 34 ± 7 ng/ml (range 21–44 ng/ml). Plasma fentanyl increased to 48 ± 8 ng/ml after 25 μg/kg and remained at approximately 50 ng/ml for the duration of the fentanyl infusion (Figure). Plasma fentanyl decreased slowly after termination of the infusion and was further decreased with initiation of cardiopulmonary bypass but was little changed with 45 or 60 additional minutes of bypass and 45 and 60 minutes after bypass.

Fentanyl (25 μg/kg) produced small by significant decreases in mean arterial, pulmonary artery, and pulmonary capillary wedge pressures, and pulmonary and systemic vascualr resistances (Table). Additional fentanyl produced no further changes in these variables. Fentanyl did not significantly change heart rate, cardiac output, or mean right atrial blood pressure at any time during the study. Administration of helium did not further alter any cardiovascular variable studied, but breathing nitrous oxide produced a significant decrease in cardiac output and significant increases in pulmonary and systemic vascular resistances and

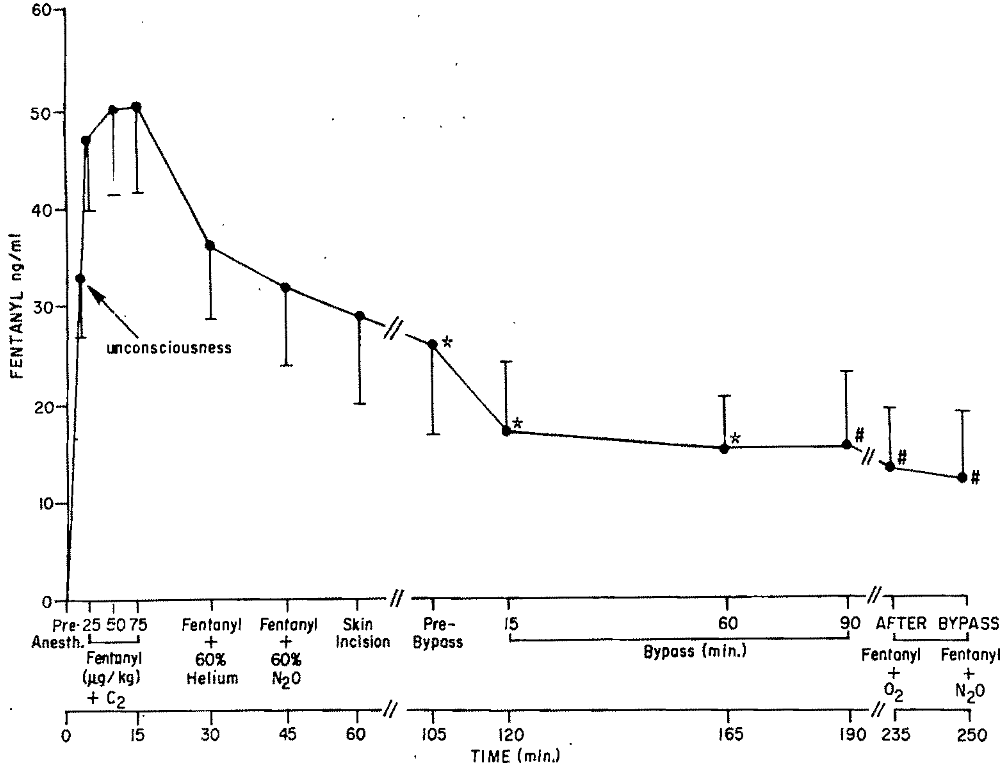

FIGURE. Plasma concentrations of fentanyl during and following intravenous administration of the compound. $^{*}p < 0.025$, $^{\#}p < 0.01$, Student's paired *t*-test when compared to values obtained following administration of 25 μg/kg of fentanyl.

TABLE

Cardiovascular Dynamics during Fentanyl Anesthesia in Man (mean ± SD)

	Pre-anesthesia (control)	Fentanyl + O_2			Fentanyl + 60% Helium	Fentanyl + 60% N_2O	Skin incision	Pre-bypass	After bypass	
		25 µg/kg	50 µg/kg	75 µg/kg					Fentanyl + O_2	Fentanyl + N_2O
Heart rate (beats/min)	64 ±8	61 ±6	60 ±5	62 ±6	63 ±7	74*† ±8	73*† ±9	73*† ±8	64 ±9	75*† ±11
Cardiac output (L/min)	4.7 ±0.6	4.6 ±0.7	4.5 ±0.6	4.5 ±0.5	4.6 ±0.5	3.1†‡ ±0.4	3.2†‡ ±0.5	3.2†‡ ±0.6	4.4 ±0.9	3.0†‡ ±0.6
Mean arterial blood pressure (torr)	107 ±12	91* ±14	87* ±13	91* ±11	86* ±13	93* ±10	99 ±13	99 ±12	89* ±14	84* ±11
Mean right atrial pressure (torr)	7 ±2	7 ±2	6 ±2	7 ±2	7 ±2	10*§ ±2	10*§ ±2	11*§ ±3	8 ±2	11*§ ±2
Mean pulmonary artery pressure (torr)	22 ±3	18* ±2	16* ±3	17* ±2	17* ±2	17* ±2	17* ±2	17* ±3	18* ±4	18* ±4
Mean pulmonary capillary wedge pressure (torr)	15 ±2	12* ±2	11* ±2	12* ±2	12* ±2	11* ±3	11* ±2	11* ±2	11* ±3	11* ±3
Pulmonary vascular resistance (dynes·sec/cm^5)	123 ±16	104* ±18	93* ±17	95* ±13	90* ±17	164†‡ ±14	169†‡ ±15	160†‡ ±19	91* ±20	160* ±16
Systemic vascular resistance (dynes·sec/cm^5)	1752 ±189	1489‡ ±174	1443‡ ±191	1493‡ ±203	1385‡ ±214	2270†‡ ±186	2291†‡ ±174	2212†‡ ±192	1473†‡ ±208	1996†‡ ±181

* $p < 0.05$, Student's paired *t*-test when compared to control values.
† $p < 0.025$, Student's paired *t*-test when compared to values at 25 µg/kg of fentanyl.
‡ $p < 0.025$, Student's paired *t*-test when compared to control values.
§ $p < 0.05$, Student's paired *t*-test when compared to values at 25 µg/kg of fentanyl.

heart rate both before operation and after cardiopulmonary bypass. Nitrous oxide did not alter pulmonary arterial or pulmonary capillary wedge pressures. Surgical stimulation including median sternotomy and pre-bypass cannulations and manipulations resulted in no further significant alteration in any cardiovascular variable studied.

Infusion of fentanyl did reduce chest wall compliance (it became more difficult to assist or control ventilation mechanically in four patients) but did not result in sufficient chest wall rigidity to impair ventilation. No other problems occurred in any of the patients.

Skin incision did not produce movement in any patient. No patient remembered any aspect of his operation, and all were extubated 2 to 8 hours after operation without any need of a narcotic antagonist.** Unfortunately, blood samples could not be obtained nor cardiovascular dynamics measured at the time of extubation.

Discussion

Plasma decay curves obtained following infusion of large doses of fentanyl in this study are in contrast to those obtained following more modest doses of the compound, especially in the early postinfusion period.[6,7] Hess and co-workers[6] found that after intravenous infusion of 200 to 500 µg of fentanyl in man (approximately 5 to 10% of the doses used in this study) plasma fentanyl concentrations rapidly declined from initial peak values and then slowly decreased thereafter. These investigators showed that 15 minutes after infusion, plasma fentanyl concentrations were only approximately 30% of peak concentrations but did not significantly change thereafter for as much as 8 hours. They explained their findings by suggesting that fentanyl undergoes rapid uptake in highly vascularized tissues and is redistributed to less vascular tissues but is only slowly metabolized and excreted in feces and urine.

In this study plasma fentanyl concentrations decreased more slowly after termination of fentanyl infusion. Fifteen minutes after the infusion was stopped (30 minutes after initiation of infusion) fentanyl plasma concentrations were more than 70% of peak concentrations and 75 minutes later (pre-bypass)

** Extubation was accomplished when patients could sustain a Pa_{CO_2} of 35 to 40 torr for at least 2 hours without mechanical assistance and had a tidal volume of at least 7 ml/kg and vital capacity of at least 15 ml/kg.

were still 50 to 60% of peak levels. Initiation of cardiopulmonary bypass produced a further decrease (37%) in plasma fentanyl concentration but little additional change occurred during the remainder of bypass or in the first 60 minutes after bypass.

The rapid onset and brief duration of analgesia observed after small intravenous doses of fentanyl are consistent with the changes in plasma fentanyl concentration observed by Hess et al[6,7] in man and the rabbit. These studies and others[8] have demonstrated that fentanyl is rapidly taken up from plasma and bound in lung, spleen, and kidney. Skeletal muscle concentrations of fentanyl also increase but not as rapidly nor to the same extent as concentrations in lung, spleen, and kidney. Only a small percentage (approximately 1%) of administered fentanyl ever reaches brain tissues in animals (rabbits) after administration of small doses of the compound (10 to 20 μg/kg) and concentrations in this organ dissipate rapidly.[7] Brain and other organ concentrations of fentanyl have not been measured after administration of larger doses of the narcotic in man. However, larger doses or repeated small doses of fentanyl have resulted in higher and longer lasting plasma concentrations in the dog,[9,10] and, our results in this study indicate, in man as well. These findings suggest that larger doses of fentanyl produce tissue accumulation and thus higher and longer lasting plasma and brain concentrations of the drug.

In this study, loss of consciousness occurred after 18 ± 4 μg/kg of fentanyl had been administered. Fentanyl doses required to produce unconsciousness in a previous report in patients with severe mitral valvular disease averaged 11 ± 3 μg, about 40% less than in this study.[1] Unfortunately, it was not possible to obtain plasma fentanyl concentrations during that investigation. Although the reason(s) for the increased doses of fentanyl required to produce unconsciousness in patients in this study are not known, one explanation could be that cardiac output, blood volume, and/or tissue distribution volumes for fentanyl were greater in this study. Interestingly, patients remained unconscious and required mechanical respiratory support after operation for similar periods of time in both this and in our previous study,[1] 8 to 12 hours and 2 to 8 hours, respectively.

Mean plasma fentanyl concentrations decreased to approximately 20 ng/ml 15 minutes after starting cardiopulmonary bypass and remained at this low level throughout bypass and for 1 hour after bypass. This change in plasma fentanyl concentration with bypass was undoubtedly due to plasma dilution by the extracorporeal priming solution. In spite of the absence of nitrous oxide and the use of no other anesthetic or central nervous system depressant during, and early after bypass, no patients was aware of any aspect of their operation when questioned postoperatively. Since plasma fentanyl concentrations during bypass were significantly lower than concentrations that produced unconsciousness during anesthetic induction, hypothermia during bypass and/or the abnormal conpulsatile circulation of bypass must have contributed to the anesthesia achieved during and after this interval. On the other hand, while plasma fentanyl concentrations decreased with the initiation of bypass, fentanyl brain concentrations may have remained unchanged. Unfortunately, it was impossible to measure brain concentrations of fentanyl in this study. However, Hess et al[7] have shown that brain concentrations of fentanyl decrease much slower than plasma concentrations following injection of 20 μg/kg in the rabbit. In contrast, Hug and Murphy[10] showed that cerebrospinal fluid concentrations of fentanyl decreased at a rate similar to plasma concentrations after 10 μg/kg of fentanyl in the dog.

Increases in heart rate and arterial blood pressure following endotracheal intubation and particularly after median sternotomy are common in patients with coronary artery disease during morphine (1 to 3 mg/kg) anesthesia.[11,12] The cause(s) of these changes has not been carefully investigated but is probably related to inadequate depth of anesthesia since the changes do not occur following higher doses of morphine (8 to 11 mg/kg)[13] Increases in heart rate and arterial blood pressure following intubation and all forms or surgical stimulation were not observed during this study. It is our opinion that these changes did not occur because the doses of fentanyl employed in this investigation (the equivalent of 7.5 to 10 mg/kg of morphine after 50 μg/kg of fentanyl, if the potency of fentanyl is 150 times greater than morphine) produced more analgesia or a greater depth of anesthesia than usually employed doses (1 to 3 mg/kg) or morphine.

Reports from this laboratory[2] and others[3,14] have demonstrated that supplementation of nitrous oxide during high dose morphine anesthesia produces cardiovascular depression. Similar degrees of cardiovascular depression have been found when nitrous oxide is added to the inspired mixture of gases given patients receiving conventional (nonanesthetic) doses of meperidine of fentanyl.[4,15] In most of these studies, cardiac output was depressed by nitrous oxide and peripheral arterial and pulmonary vascular resistances increased. Lappas and co-workers[14] have shown that nitrous oxide has a negative myocardial inotropic effect after morphine. A similar mechanism probably explains the cardiovascular depression found when nitrous oxide is added after administration of fentanyl or meperidine.

Supplementation with nitrous oxide after fentanyl administration in this study produced cardiovascular changes similar to those previously reported when nitrous oxide was combined with morphine, meperidine, and smaller doses of fentanyl.[2-4,14,15] Decreases in cardiac output and increases in pulmonary and systemic vascular resistances were the same in this investigation both before operation (when plasma concentrations of fentanyl averaged 32 ± 7 ng/ml) and after bypass (when plasma concentrations of fentanyl averaged 12 ± 7 ng/ml). These findings indicate that plasma concentrations of fentanyl (at least those above 12 ng/ml) have little influence on the magnitude of cardiovascular depression produced by addition of nitrous oxide during fentanyl-oxygen anesthesia.

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58:396-400, 1979

Comparison of Domperidone, Droperidol, and Metoclopramide in the Prevention and Treatment of Nausea and Vomiting after Balanced General Anesthesia

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KORTTILA, K., KAUSTE, A., AND AUVINEN, J: Comparison of domperidone, droperidol, and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. Anesth Analg 58:396-400, 1979.

Women (185) undergoing elective orthopedic surgery under balanced general anesthesia were given 5 or 10 mg of domperidone, 1.25 mg of droperidol, 10 mg of metoclopramide, or a saline placebo intravenously in a double-blind random fashion 5 minutes before the end of anesthesia to prevent postoperative vomiting. Administration of the same antiemetic was repeated intramuscularly during the first 24 hours postoperatively if the patient complained of nausea or retched or vomited. Significantly ($p < 0.05$ to $p < 0.001$), fewer of the patients given droperidol were nauseated (25%) or vomited (17%) in comparison with patients given saline (incidence of nausea was 55% and vomiting 40%). Incidences of nausea and vomiting were similar in patients given domperidone, metoclopramide, or saline. Furthermore, 39 to 45% of the patients given domperidone, metoclopramide, or saline needed additional doses of the same drug, whereas only 22% of the patient given droperidol required a second dose. It is concluded that droperidol is effective in the prevention and treatment of postoperative nausea and vomiting after balanced general anesthesia but that domperidone or metoclopramide are not.

Key Words: VOMITING: antiemetics.

POSTOPERATIVE nausea and vomiting are quite common after general anesthesia,[1-4] and the prophylactic administration of antiemetics has been suggested for those patients most prone to vomiting.[4]

Domperidone is a new benzimidazole antiemetic. It is assumed to prevent and treat nausea and vomiting by increasing the motility of the upper gastrointestinal tract and by having a direct antiemetic effect on the chemoreceptor trigger zone [5,6] It has been reported to be effective in the treatment of chronic dyspepsia[7] and in the prevention of postoperative nausea and vomiting.[6]

In this study, we have compared the antiemetic efficacy of domperidone in the prevention and treatment of postoperative nausea and vomiting to that of droperidol and metoclopramide, both of which have previously been reported to decrease the incidence of postoperative nausea and vomiting.[8-10]

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Materials and Methods

Patients and Anesthesia

We studied 185 women undergoing elective orthopedic surgery (Table 1). All of the patients belonged to A.S.A. class I-II and during the 2 weeks prior to the operation none had taken any drugs with an antiemetic action. Informed consent was obtained from each patient. For premedication, all patients received 0.15 mg/kg of oxycodone chloride intramuscularly for 40 to 60 minutes and 0.01 mg/kg of atropine intravenously for 5 minutes before the induction of anesthesia. Anesthesia was induced with a sleep dose of thiopental and maintained by supplementation of nitrous oxide-oxygen (33%) with fentanyl and alcuronium chloride to provide adequate analgesia and muscle relaxation. Endotracheal intubation was facilitated by 1.5 mg/kg of succinylcholine after a small "precurarizing dose" of alcuronium. At the end of anesthesia, 0.03 mg/kg of neostigmine chloride was given with atropine, 0.015 mg/kg, to reverse the muscle relaxation. For moderate to severe postoperative pain, oxycodone chloride, 0.15 mg/kg was given intramuscularly.

Administration of Antiemetics

Five minutes before the end of anesthesia, the patients were given intravenously a 2-ml solution which consisted of 5 or 10 mg of domperidone (R 33 812, Janssen, Beerse), 1.25 mg of droperidol, 10 mg of metoclopramide (Emperal, Neofarma, Seinajcki), or a saline placebo in a double-blind randomized fashion.

In addition to the prophylactic administration of the antiemetics, the same antiemetic, in the same amount, was given intramuscularly if the patient complained of nausea or retched or vomited during the first 24 postoperative hours.

If the test drug did not allevaite emesis even though the dose had been repeated once, the patients were given 1.25 mg of droperidol 30 minutes after the second intramuscular dose of the test drug.

To determine the effects of the three antiemetics studied on emergence from anesthesia, we measured the time elapsed after the cessation of nitrous oxide administration until the patients opened their eyes after repeated commands. Side effects were registered during the first 2 postoperative hours in the recovery room by monitoring the patients' consciousness, muscle activity, respiration, circulation, and color every 15 minutes.[11] During the subsequent 22 hours in the ward, these functions were monitored every 2 hours and every 30 minutes for the 2 hours following a possible administration of additional doses of antiemetics.

Assessment of Emetic Sequelae

The incidence of nausea and vomiting was determined for the first 24 hours after operation at different intervals: 0 to 3, 3 to 6, 6 to 12, 12 to 18, and 18 to 24 hours. At the end of each interval, a trained nurse registered whether retching or vomiting had occurred and asked the patients whether they felt nauseated. The results were scored in a manner similar to that of Bellville et al[12] (0 = none, 1 = nausea, 2 = retching, 3 = vomiting).

Statistics

Student's t-test was used for the comparisons made between the characteristics of the patients and anesthesia. The chi-square test was used to compare the efficacy of the antiemetics because of the nonparametric nature of the data.

Results

The principal result was that only droperidol decreased the incidence of nausea and vomiting when compared to the saline placebo; domperidone or metoclopramide did not.

TABLE 1

Characteristics of the Test Groups (means ± SD)

Treatment	No. of patients	Age	Weight	Height	Duration of anesthesia	Thiopental	Alcuronium	Fentanyl
		yr	*kg*	*cm*	*min*	*mg*	*mg*	*mg*
Domperidone, 5 mg	36	40 ± 13	61 ± 10	162 ± 5	94 ± 30	347 ± 68	19 ± 4	0.29 ± 0.10
Domperidone, 10 mg	36	42 ± 13	64 ± 10	161 ± 6	78 ± 28	347 ± 56	18 ± 3	0.27 ± 0.16
Droperidol, 1.25 mg	36	43 ± 14	64 ± 12	163 ± 7	107 ± 42*	350 ± 75	21 ± 5	0.33 ± 0.11
Metoclopramide, 10 mg	37	41 ± 14	61 ± 10	162 ± 6	85 ± 28	339 ± 71	17 ± 3	0.25 ± 0.08
Saline	40	41 ± 13	62 ± 10	162 ± 6	95 ± 51	334 ± 51	19 ± 4	0.31 ± 0.17

* $p < 0.05$ vs domperidone, 10 mg, and vs metoclopramide.

The amount of thiopental needed for induction was similar in each group, as were the amounts of alcuronium required for muscle relaxation and the doses of fentanyl and oxycodone administered for operative and postoperative pain, respectively (Tables 1 and 2). The duration of anesthesia and the time elapsed until the patients opened their eyes at the end of anesthesia were longest in patients given droperidol (Tables 1 and 2). No clinically significant side effects were observed in any patient after the administration of any of the antiemetics, either in the recovery room or in the ward.

Fig 1 shows the incidence of emetic sequelae during the 24-hour follow-up period in the different test groups. Significantly fewer of the patients given droperidol felt nauseated (25%) or vomited (17%) in comparison with control patients given saline (incidence of nausea was 55% and of vomiting 40%). The incidences of nausea and vomiting in patients given domperidone or metoclopramide were similar to those in control patients. As shown in Fig 2, nausea and vomiting were most common between 3 and 12 hours after anesthesia.

TABLE 2

Postoperative Awakening and Amount of Postoperative Analgesia (Oxycodone) Needed in First 24 Hours (means ± SD)

Treatment	Eyes open	Oxycodone
	min	*mg*
Domperidone, 5 mg	2.03 ± 1.87	23 ± 10
Domperidone, 10 mg	1.95 ± 1.43	24 ± 9
Droperidol, 1.25 mg	2.48 ± 1.70*	22 ± 15
Metoclopramide, 10 mg	1.49 ± 0.59	24 ± 10
Saline	1.45 ± 0.75	20 ± 10

* $p < 0.05$ vs saline.

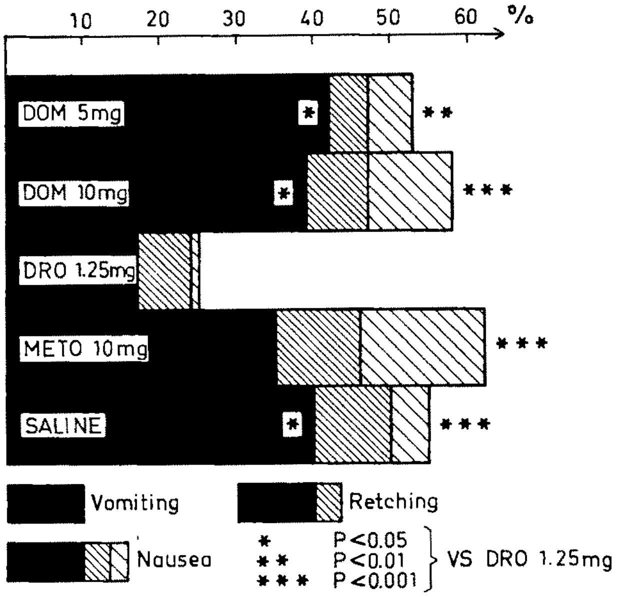

FIG 1. Incidences of postoperative nausea and vomiting after balanced general anesthesia and the prophylactic and therapeutic administration of domperidone (DOM), droperidol (DRO), metoclopramide (METO), or a saline placebo in women undergoing elective orthopedic surgery.

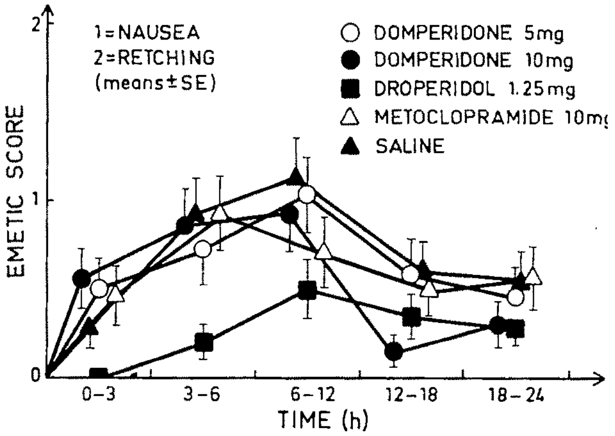

FIG 2. Postoperative emetic score as a function of time after balanced general anesthesia in patients undergoing elective orthopedic surgery.

As shown in Fig 3, 39 to 45% of the patients given domperidone, metoclopramide, or saline needed additional doses of the same drug, while only 22% of the patients given droperidol needed a repeated dose. None of the patients receiving droperidol as a blind drug needed to be given additional droperidol as a known antiemetic because of failure of the blind drug to prevent or treat emetic symptoms; however, 8 to 14% of the patients given domperidone, metoclopramide, or saline as the blind drug were also given an additional dose of droperidol (Fig 3).

Discussion

In our present investigation, only droperidol significantly decreased the incidence of postoperative nausea and vomiting in comparison to the corresponding incidence after a saline placebo. Nausea and vomiting were not reduced by either domperidone or metoclopramide.

Trial Design

A comparison of the antiemetic efficacy of the drugs studied is justified in this investigation, since the variables modifying the incidence of nausea and vomiting, i.e., age, sex, type and duration of anesthesia, type of operation, and the amount of narcotic analgesics given,[1-4] were similar in each group. The groups differed only in respect to the antiemetic

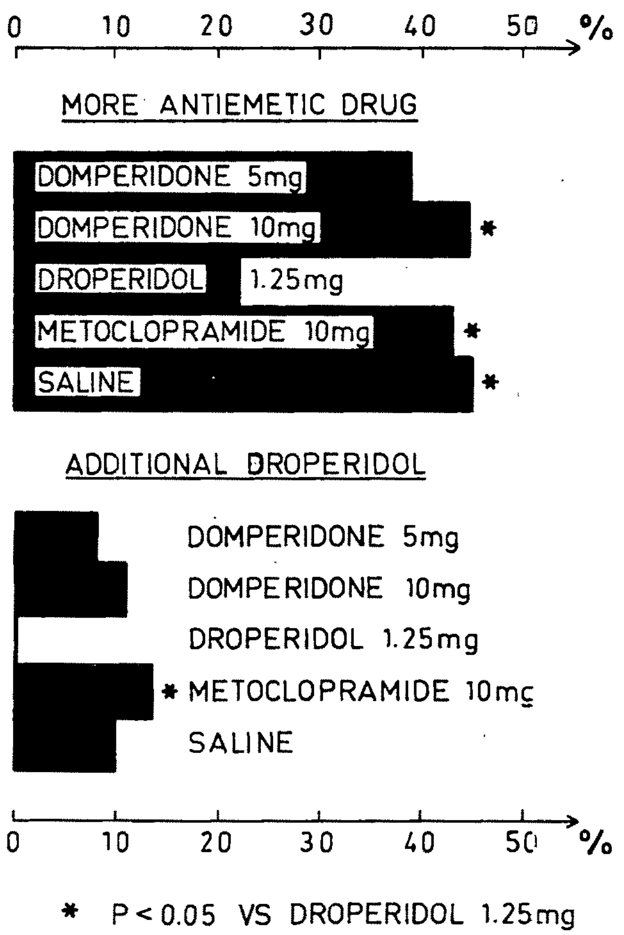

FIG 3. Incidences of patients needing more than one injection of antiemetic and of those needing additional droperidol as a known antiemetic during the 24-hour follow-up period because of the failure of the repeated administration of the blind drug to alleviate nausea and vomiting.

given. The slightly longer duration of anesthesia, as well as the slightly greater amount of fentanyl, in patients given droperidol should have contributed to a higher incidence of emetic sequelae than that associated with shorter duration of anesthesia and a smaller amount of fentanyl.[2,3]

A 1969 National Research Council report stated that evidence of the prophylactic effectiveness of an antiemetic agent does not imply that it is effective therapeutically.[13] Since the patients in this study belonged to a patient group prone to vomiting after anesthesia and since it had been recommended that they be given antiemetics prophylactically after anesthesia,[4] we administered the antiemetics both prophylactically at the end of anesthesia and therapeutically when the patients vomited or complained of nausea during the postoperative period.

The doses of drugs used were based on reports in the literature[5,6,9,10,14,15] on the antiemetic efficacy in the treatment of postoperative nausea and vomiting. The scoring of nausea and vomiting used in this study has previously proven useful in a comparison of the antiemetic efficacy of drugs during the postoperative period.[2-14,16]

Effect of Metoclopramide and Domperidone

In healthy volunteers, the intravenous injection of 10 mg of metoclopramide increases gastric emptying for at least 3 hours.[17] The efficacy of metoclopramide in the treatment of postoperative nausea and vomiting is controversial. Lind and Breivik[9] noticed significantly less nausea, retching, and vomiting in women given 10 mg of metoclopramide intramuscularly before undergoing minor gynecological laparotomies under thiopental-nitrous oxide-oxygen-halothane anesthesia than in women receiving 5 mg of perphenazine before undergoing the same type of operation. Tornetta[10] also found that 20 mg of metoclopramide administered intravenously or intramuscularly prevented postoperative emetic symptoms after general anesthesia for elective general surgery. On the other hand, Ellis and Spence[18] and Shah and Wilson[19] found neither 10 or 20 mg of metoclopramide, given intramuscularly or intravenously, to be more effective than a placebo in preventing nausea and vomiting in women undergoing minor gynecologic operations under cyclopropane or thiopental-nitrous oxide-oxygen halothane anesthesia.

As mentioned above, the antiemetic effect of domperidone is assumed to be due to its ability to increase the motility of the upper gastrointestinal tract, as well as to its direct action on the chemoreceptor trigger zone. Fragen and Caldwell[6] reported the recurrence of nausea and vomiting to be less frequent when women undergoing gynecologic surgery under balanced or enflurane anesthesia were given 10 mg of domperidone intravenously after vomiting rather than a placebo. In a multicenter study by Zegveld et al,[14] when 10 mg of domperidone or a placebo was given after patients had vomited after different types of general anesthesia, significantly more patients needed additional antiemetic after the placebo than after the domperidone during the 6-hour follow-up period. In our study, neither metoclopramide nor domperidone was better than the placebo in preventing and treating postoperative emetic sequelae. This finding may indicate that drugs with an antiemetic efficacy based mainly on their ability to increase gastrointestinal motility may not be clinically useful during the postoperative period when the gastrointestinal tract is hypoactive, especially if atropine or large quantities of narcotic analgesics were used during the anesthesia. Thus, our results with metoclopramide and domperidone are not directly applicable to other clinical situations, which should be tested separately.

Effects of Droperidol

In the original studies of droperidol by Janssen et al,[19] droperidol was shown to have a potent antiemetic effect. In many clinical reports,[8,15,21] droperidol has been shown to have a good postoperative antiemetic effect.

Our finding that droperidol was significantly better than placebo in preventing and treating postoperative nausea and vomiting agrees with the literature cited and suggests that droperidol prevents both the occurrence and recurrence of postoperative nausea and vomiting.

The lack of side effects after the administration of droperidol in this study was apparently due to the small dose of droperidol used. If larger doses of droperidol are used or if its administration is repeated frequently, the prevention of nausea and vomiting can be expected to be associated with circulatory changes[22] and with prolonged sense of tiredness.[23]

In summary, droperidol can be recommended for the prevention and treatment of postoperative nausea and vomiting, whereas drugs creating antiemetic effects by modifying the motility of the gastrointestinal tract, e.g., metoclopramide or domperidone, are ineffective in this respect, at least after balanced general anesthesia.

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Epinephrine-Induced Arrhythmias: Effect of Exogenous Prostaglandins and Prostaglandin Synthesis Inhibition during Halothane-O_2 Anesthesia in the Dog

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PACE, N. L., OHMURA, A., AND WONG, K. C.: Epinephrine-induced arrhythmias: effect of exogenous prostaglandins and prostaglandin synthesis inhibition during halothane-O_2 anesthesia in the dog. Anesth Analg 58:401-404, 1979.

Prostaglandins (PG) modify sympathetic and parasympathetic neurotransmission and have antiarrhythmic properties. Inhibitors of PG synthesis sensitize the heart to certain experimentally induced arrhythmias. This study examined the arrhythmogenic dose (AD) of epinephrine in dogs during halothane-O_2 anesthesia as modified by the infusion of PG and by treatment with an inhibitor of PG synthesis.

Dogs were anesthetized with 1.25 MAC halothane. The AD of epinephrine was established by a series of 3-minute epinephrine infusions at 10-minute intervals. The AD of epinephrine was then redetermined during infusions of PG (PGE_1—1 μg/kg/min and PGF_2 alpha—1 μg/kg/min), after indomethacin, 3 mg/kg, and after aminophylline, 10 mg/kg. The AD remained unchanged from control during both of the PG infusions and following indomethacin. Only following aminophylline did the AD decrease significantly.

Our study suggests that pretreatment of surgical patients with nonsteroidal antiinflammatory drugs which inhibit PG synthesis does not increase the likelihood of ventricular arrhythmias during halothane-O_2 anesthesia.

Key Words: HORMONES: prostaglandins; HEART: arrhythmias; ANESTHETICS, Volatile: halothane.

ADRENAL EXTRACT was first shown to produce ventricular fibrillation in a dog anesthetized with chloroform in 1895.[1] Since then there have been many studies evaluating the arrhythmogenecity of anesthetics. A common technique has been to observe the appearance of ventricular extrasystoles following incremental doses of intravenous epinephrine. The use of epinephrine has particular clinical relevance in anesthesia because intraoperative cardiac arrhythmias are frequently associated with an imbalance of the autonomic nervous system, usually a preponderance of sympathetic activity. In addition, epinephrine is commonly used topically or subcutaneously to reduce surgical bleeding.

Today's commonly used anesthetics have widely different sensitizing effects on the myocardium. For example, Joas and Stevens[2] showed in their study of the dog that under equipotent amounts of anesthetic agent the arrhythmogenic dose (AD) of epinephrine during halothane anesthesia was 5 μg/kg whereas

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with equipotent concentrations of fluroxene the AD was 43 μg/kg. In the same study the AD in the awake state was the same as during fluroxene anesthesia. Thus, fluroxene had no protective effect, but halothane sensitized the heart to the arrhythmogenic effect of epinephrine. In general, halogenated ethers do not sensitize, whereas the halogenated hydrocarbons do sensitize the myocardium.

During the last decade there has been an increasing interest in a family of substances derived from essential fatty acids, the prostaglandins (PG), which play a significant role in the regulation of many cellular processes.[3] Prostaglandins can be found in all body tissues. They are synthesized under the influence of the enzyme prostaglandin synthetase from the precursor fatty acids dihomo-gamma-linolenic acid and arachidonic acid. The half-life of the prostaglandins (PG) in the body is short, 90 to 100% being broken down during one passage through the liver and lungs. Their physiologic activities are exerted at the cellular level and are probably limited to the organ where they are produced. The mechanisms of action of prostaglandins are still unclear, but may include regulation of cyclic AMP and cyclic GMP. Another important finding is the inhibition of prostaglandin synthetase by the common nonsteroidal antiinflammatory drugs such as aspirin and indomethacin.

Prostaglandin PGE_1 has been shown to inhibit sympathetic and parasympathetic neurotransmission in the isolated innervated rabbit heart.[3] Another PG, PGF_2 alpha, does not show this effect.[3] In contrast, inhibitors of PG synthesis increase the release of norepinephrine per nerve impulse at autonomic nerve terminals as a consequence of inhibition of local PGE formation.[4] Both PGE_1 and PGF_2 alpha have anti-arrhythmic effects in experimentally induced arrhythmias. PGE_1 suppresses spontaneous ventricular bigeminy in anesthetized dogs[5] and in cats significantly increases the dose of ouabain necessary to produce premature ventricular complexes, ventricular tachycardia, and death;[6] animals were anesthetized with barbiturates. PGF_2 alpha had anti-arrhythmic effects in rats challenged with calcium chloride and aconitine, in cats given ouabain, and in rabbits receiving barium chloride.[7] Inhibitors of prostaglandin synthesis have been shown to lower the dose of ouabain required to cause ventricular fibrillation in the dog.[8] The effect of PG and PG synthesis inhibition on epinephrine-induced arrhythmias is unknown. Equally unknown and unpredictable is any possible interrelationship of halogenated anesthetics and PG synthesis and PG synthesis inhibition on arrhythmogenicity. Since the mechanisms of cardiac glycoside and of epinephrine arrhythmias are different,[9,10] a differential anti-arrhythmic effect of PG and PG synthesis inhibition is possible.

The objective of our study was to examine the sensitivity of the dog myocardium to experimental arrhythmias during inhalational anesthesia as modified by the infusion of PG and by pretreatment with an inhibitor of prostaglandin synthesis.

Methods

Six, fasted mongrel dogs of either sex, weighing approximately 20 kg each, were anesthetized with thiopental, 20 mg/kg. The trachea was intubated with a tightly fitting cuffed endotracheal tube without use of skeletal muscle relaxants. The dogs were mechanically ventilated at a tidal volume of 15 ml/kg at a respiratory rate sufficient to maintain Pa_{CO_2} at levels of 35 to 40 torr. Anesthesia was maintained with 1.25 MAC halothane in 30% O_2 with the balance being N_2. (In the dog, halothane MAC is 0.87%.)[11] Inspired O_2 concentrations were monitored with an O_2 analyzer.

End tidal anesthetic and CO_2 concentrations were measured continuously with two infrared gas analyzers. Rectal temperature was monitored and body temperature maintained at 37–39 C with a heating lamp and heating blanket. A foreleg vein was cannulated for administration of drugs and salt and dextrose solutions. A femoral arterial catheter was placed for arterial blood sampling and continuous pressure monitoring; lead II of the ECG was also continuously recorded.

After a 45-minute equilibrium period, the AD of epinephrine was determined in the following way. Freshly mixed epinephrine was prepared for each dog in order to allow the continuous infusion of epinephrine according to a list of predetermined, logarithmically spaced doses (0.67, 0.82, 1.00, 1.22, 1.49, 1.82, 2.23, 2.72, 3.32, 4.06, 4.95 μg/kg/min). If arrhythmias did not develop after 3 minutes of a constant epinephrine infusion with one concentration, the infusion was terminated and the dog given 10 minutes to recover. The next higher epinephrine dose was then infused for 3 minutes, followed by a 10-minute rest. This procedure was repeated until the AD was reached. The epinephrine AD is the dose (μg/kg/min) which produced four or more continuous or intermittent premature ventricular contractions within 15 seconds during a three-minute infusion. Heart rate and arterial blood pressure were also recorded.

Two prostaglandins (PGE_1 and PGF_2 alpha) were infused in each dog; the order of administration was varied. Stock solution of PGE$_1$ and PFG$_2$ alpha (10 mg/ml in absolute ethanol) were prepared. Fresh dilute aqueous solutions (50 µg/ml in normal saline) were prepared daily. PGE$_1$ or PGF$_2$ alpha were infused intravenously at a rate of 1.0 µg/kg/min. Ten to 20 minutes were allowed between the two PG infusions; the rapid pulmonary clearance of PG allow dissipation of effect within minutes.

Each dog received indomethacin dissolved in normal saline by adjusting the pH into the alkaline range by titration with 0.1 N Na_2CO_3.[8] All solutions were prepared immediately prior to each study. Indomethacin was given 10 to 20 minutes after the second PG infusion. The calculated dose of indomethacin, 3 mg/kg, was diluted to a final volume of 10 ml and infused intravenously over 3 to 5 minutes.[8] (Indomethacin suppression of PG synthesis lasts hours.) Each dog also received aminophylline, 10 mg/kg, intravenously over 8 minutes.[12]

The arrhythmic epinephrine dose was determined in the following sequence: (1) control; (2) during PGE$_1$ infusion, 1 µg/kg/min; (3) during PGF$_2$ alpha infusion, 1 µg/kg/min; (4) 30 minutes after indomethacin, 3 mg/kg; (5) 10 minutes after aminophylline, 10 mg/kg.

Comparisons of log epinephrine AD, change in heart rate, and change in mean arterial pressure were determined by a two-way analysis of variance without replication; statistical significance was set at $p < 0.05$.

Results

The AD was 2.07 µg/kg/min during halothane anesthesia (Table). This did not change with PGE$_1$ infusion, PGF$_2$ alpha infusion or following indomethacin. After aminophylline, 10 mg/kg, the AD dose decreased significantly ($p < 0.01$).

Changes in heart rate and mean arterial pressure associated with infusion of epinephrine were the same during infusions of PGE$_1$, PGF$_2$ alpha, after indomethacin, and after aminophylline as they were during infusion of epinephrine in the control state. There was always the same large increase in blood pressure and slight decrease in heart rate.

Discussion

The ability of epinephrine to produce arrhythmias is attributed to its action at adrenergic receptors.[10] The response to epinephrine is thus dependent in large part on catecholamine terminating mechanisms. In fact, agents inhibiting catecholamine reuptake into adrenergic nerve endings (cocaine and ketamine), inhibition of extraneuronal uptake with O-methylation by COMT (tropolone), and inhibition of the inactivation of cyclic AMP by phosphodiesterase (aminophylline) all lower the arrhythmic threshold.[12]

The mechanism for halothane-catecholamine induced arrhythmias is thought to involve changes in refractory periods and conduction velocities allowing conditions for re-entry excitation;[13] changes in automaticity are also possible.[13] Fasting,[14] hypertension,[15] and rapid heart rate[16] have all been demonstrated as predisposing factors that facilitate arrhythmias. Skeletal muscle relaxants have been shown to have antiarrhythmic effects.[17]

These experiments were designed to reflect these modifying influences. All dogs had the same overnight fast. No skeletal muscle relaxants were used. The responses of heart rate and blood pressure to epinephrine infusion were examined and remained the same during control and the four experimental conditions. The infusion doses of PGE$_1$ and PGF$_2$ alpha (1 µg/kg/min) were of the same magnitude as those previously shown to have antiarrhythmic effects.[5,7] As there are no tissue stores of prostaglandins, a 30-minute period following indomethacin (3 mg/kg) was considered sufficient to block prostaglandin synthetase and endogenous prostaglandin release.[18] Because indomethacin (3 mg/kg) might also inhibit phosphodiesterase,[18] it was decided to give amino-

TABLE
Results during Halothane Anesthesia

	Epinephrine threshold dose (µg/kg/min)		Change in heart rate (beats/min; mean ± SEM)	Change in mean arterial pressure (torr; mean ± SEM)
	Mean	95% confidence interval of the mean		
Control	2.07	1.73–2.48	−7.3 ± 11.0	92.3 ± 13.2
PGE$_1$ (1 µg/kg/min)	2.30	1.85–2.88	−9.8 ± 13.8	105.7 ± 7.7
PGF$_2$ alpha (1 µg/kg/min)	2.12	1.68–2.66	−9.8 ± 8.0	93.7 ± 8.1
Indomethacin (3 mg/kg)	2.22	1.76–2.79	−28.8 ± 8.5	102.5 ± 9.1
Aminophylline (10 mg/kg)	1.16	0.97–1.39	−15.8± 11.7	83.8 ± 10.9

phylline, a known phosphodiesterase inhibitor, in a dose (10 mg/kg) previously shown to lower the epinephrine threshold.[12] It was thought that if any lowering of the epinephrine threshold with indomethacin resulted, the possibility of a contribution by phosphodiesterase inhibition could be determined by the response to aminophylline. Our results confirm the previous report[12] on the effect of aminophylline on arrhythymic thresholds.

A recent review of the role of prostaglandins in autonomic transmission concluded that while PGE_1 modulates release of norepinephrine it has no effect on reuptake or metabolism and, furthermore, that inhibitors of prostaglandin synthesis increase neuronal norepinephrine release.[4] PGF_2 alpha effects are less well understood.[4] As no change in halothane/epinephrine arrhythmias was seen, the interaction of prostaglandins and halothane is not defined in the present study.

Prostaglandins have been rarely used during general anesthesia in humans. One study in women who were anesthetized with halothane and given PGF_2 alpha at doses of approximately 1 μg/kg/min failed to show any changes in hemodynamics or cardiac rhythm.[19] Although nonsteroidal antiinflammatory drugs are not used during general anesthesia, it is not infrequent for patients coming to surgery to have been treated with these drugs. We are unaware of reports in humans of cardiac arrhythmias during anesthesia produced by these drugs. Our results are compatible with the absence of any reported toxicity and suggest that any interactions are minor compared to other known influences on halothane-epinephrine induced arrhythmias.

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Nitrous Oxide: Effect on Accumulation Rate and Uptake of Bowel Gases

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STEFFEY, E. P., JOHNSON, B. H., EGER, E. I., II, AND HOWLAND, D., JR.: Nitrous oxide: effect on accumulation rate and uptake of bowel gases. Anesth Analg 58:405–408, 1979.

Breathing 79% nitrous oxide (N_2O) in oxygen increased the rate of accumulation of bowel gas during intraluminal bowel segment infusions of hydrogen, methane (CH_4), air, or carbon dioxide (CO_2) in four pentobarbital-anesthetized dogs more than did breathing 100% oxygen. A N_2O-associated increase in the volume of naturally produced intestinal gas in five halothane-anesthetized ponies corroborated the findings in the dog studies. In a second group of four dogs a bolus of CH_4 or CO_2 was injected into the bowel lumen. When the dogs breathed O_2 the bowel gas volume decreased. Gas was virtually absent in the CO_2-containing segment within 20 minutes. Breathing N_2O increased the volume of the segments containing CH_4 while the CO_2 segments decreased less rapidly than during O_2 breathing. Breathing O_2 after 30 minutes of N_2O breathing caused little change in the rate of decrease in CO_2 segment volumes. However, the CH_4 segment volume ceased to increase and eventually returned toward control volumes.

Key Words: ANESTHETICS, Gases: nitrous oxide; GASTROINTESTINAL TRACT: intestine.

GASTROINTESTINAL and abdominal distension may occur in humans,[1,2] dogs,[3,4] and horses,[5] during nitrous oxide (N_2O)-oxygen (O_2) anesthesia. Intestinal volume expansion occurs because the greater solubility of N_2O in biologic solvents compared to that of bowel gases such as nitrogen (N_2), hydrogen (H_2), and methane (CH_4) results in a greater net transfer of N_2O molecules into the intestine.[3] Intestinal distension may also depend upon the intraluminal dilution by N_2O of locally produced bowel gases.[6] The dilution of intestinal gases by transluminal movement of N_2O would diminish the partial pressure of the intraluminal bowel gases, consequently decrease their uptake by blood, and thereby increase intraluminal gas accumulation rate.

The present study demonstrated that in dogs, breathing 79% N_2O augments the accumulation rate of bowel gas when CH_4, H_2, air, or CO_2 are infused or injected into bowel segments. We also demonstrated that breathing N_2O augmented the accumulated volume of naturally produced bowel gas in isolated bowel segments of halothane-anesthetized ponies.

Methods and Materials

Eight dogs of mixed ages and breeding and weighing 17.2 to 24.5 (20.6 ± 1.0, $\bar{X} \pm SE$) kg each, were

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divided into two groups of four each. Each dog was fasted for 12 hours, anesthetized with intravenous pentobarbital, and positioned in dorsal recumbency on a heating blanket. Normal esophageal temperature was maintained. Tracheal intubation was performed with a cuffed oro-endotracheal tube and intermittent positive pressure ventilation was controlled to produce a normal end-tidal or arterial carbon dioxide tension ($P_{ET}CO_2$, P_{CO_2}) as measured intermittently by an infrared technique or Severinghaus electrode. The dogs breathed 100% O_2 or 21% O_2 balance N_2O from a standard semiclosed circle CO_2 absorber system. Inspired O_2 concentration was measured with a Beckman D-2 O_2 analyzer. Gas delivery rates were always at least 3 L/min. Blood pressure was determined via a catheter placed percutaneously in the right femoral artery. The saline-filled catheter was attached to a Statham stain gauge transducer connected to a Grass polygraph. Systolic arterial pressure was always greater than 100 mm Hg. Lactated Ringer's solution was administered at a rate of 5 ml/kg/hr via the cephalic vein.

In all dogs a ventral midline abdominal incision was made and four contiguous 25- to 35-cm segments of distal small bowel were isolated by purse-string ties. The distal portion of the terminal segment was at the ileocecal junction. Care was taken not to injure the local blood supply. A catheter with multiple perforations was inserted into each bowel segment.

In the dogs in group I the prepared bowel was flushed clean with warm isotonic saline, and 20 ml (ambient temperature and pressure, dry (ATPD)) of H_2, CH_4, air, or CO_2 was injected into each of the four segments at rates of 0.4, 1.0, 2.0 or 4.0 ml/min. All four gas infusion rates were studied in each dog while they first breathed O_2 and then O_2-N_2O. We allowed at least 30 minutes between the O_2 and O_2-N_2O studies for equilibrations. Immediately following completion of the gas injections each bowel segment was evacuated by glass syringe. The withdrawn gas volume was measured and corrected to ATPD, and the gas accumulation rate calculated. The results for each gas and infusion rate were averaged (±SE). A linear regression relating the intraluminal gas accumulation rate to the injection rate was determined by the method of least squares. All curves were tested to determine whether a statistically significant correlation was present. The resultant data were also analyzed by analysis of variance, and a test for deviation of parallellism was performed for each injected gas.[7]

In the dogs in group II we injected a 10- or 40-ml (ATPD) bolus of CH_4 or CO_2 into each of four similarly prepared, distal small bowel segments. At 5-minute intervals (to 30 minutes) the intestinal gas was totally evacuated from each segment, measured, and immediately reinjected. Similar to dogs in group I these dogs first breathed O_2 then O_2-N_2O. However, unlike group I animals after 30 minutes of O_2-N_2O breathing, N_2O was discontinued and the dogs breathed 100% O_2 for an additional 30 to 40 minutes. The resultant bowel gas in each segment (expressed as a percent change from the initial volume) was averaged (±SE) for all dogs and plotted on a linear scale vs sampling time.

We also measured the accumulated volume of locally produced bowel gas in isolated large bowel segments of five grade ponies during halothane-O_2 or halothane and 30% O_2-balanced N_2O anesthesia. Ponies were selected because of their availability and the expected high rate of postprandial intraintestinal gas production. Their ages ranged from 4-7 years and their estimated weight averaged 140 kg. For at least 24 hours prior to study all ponies were twice offered a quality commercial grain mixture. Alfalfa hay and water were available to them at all times. On the morning of study anesthesia was induced with an intravenous injection of thiamylal sodium (7 to 10 mg/kg). Orotracheal intubation was performed with a cuffed 20-mm red rubber equine tracheal tube. Intermittent positive pressure ventilation was controlled with a locally constructed "bag in box" ventilator powered by a Bird Mark IX ventilator. Arterial P_{CO_2} was maintained normal and Pa_{O_2} was usually greater than 90 mm Hg throughout the studies. The animals were positioned in dorsal recumbency and anesthesia was maintained with halothane (1%, end-tidal). Direct carotid arterial blood pressure was continuously monitored and systolic pressure was usually greater than 100 mm Hg. A 30- to 40-cm segment of ventral large colon was isolated via a ventral midline abdominal incision. Segments of bowel containing large amounts of food material were selected. After inserting a catheter into the isolated bowel segment all resident gas was removed by syringe. The accumulated gas volume at 60 (n = 4) or 90 (n = 1) minutes was measured and recorded. Measurements were made starting from zero volume with the animals first breathing O_2 and then 30% O_2-balance N_2O. Deep abdominal temperature was monitored by thermistor.

Results

The average accumulation rate for N_2, H_2, and CH_4

in dogs in group I breathing O_2 was substantially greater than for CO_2 (Fig 1). Breathing N_2O accelerated the accumulation rate of all gases. The deviation of the two curves from parallelism was significant for all four injected gases. The greatest change occurred in the CO_2-containing segments where gas accumulation rate more than doubled.

When the dogs in group II breathed O_2 the bowel volume decreased (Fig 2). The magnitude of decrease did not depend upon the volume of gas injected but was markedly influenced by the type of gas injected. Gas was virtually absent in the CO_2-containing intestinal segment 20 minutes after injection while greater than 80% of the initial volume remained in the CH_4 segments. When O_2-N_2O was inhaled, the CH_4 segment volume increased while the volume of the CO_2 containing bowel segment decreased less rapidly than during O_2 breathing. Not surprisingly the percent change in gas volume from control was usually greatest in those CO_2- and CH_4-containing segments with the smaller initial volume.

Breathing O_2 after 30 minutes of O_2-N_2O caused little change in the rate of decrease in volume of the CO_2-containing bowel segment (Fig 2). After the change over to O_2 breathing, the volume of gas in the CH_4 segments ceased to increase and eventually returned toward control volumes. In all ponies, N_2O breathing increased the rate at which gas accumulated (Table 1).

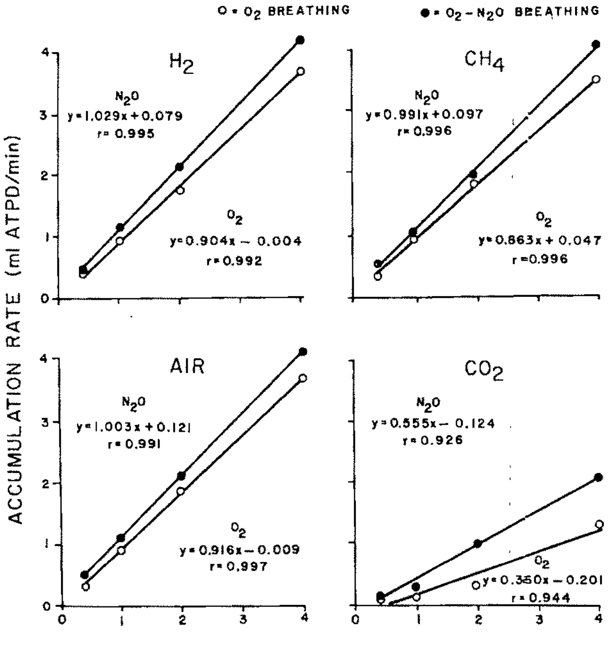

FIG 1. Composite of the intestinal lumen gas accumulation rate and injection rate relationship for hydrogen (H_2), methane (CH_4), air, and carbon dioxide (CO_2) during 100% O_2 (O_2) and 21% O_2 balance N_2O (O_2-N_2O) breathing. Each point represents the results from four dogs. The equation of lines of best fit and the correlation coefficients (r) are indicated. All correlation coefficients are highly significant ($p < 0.001$).

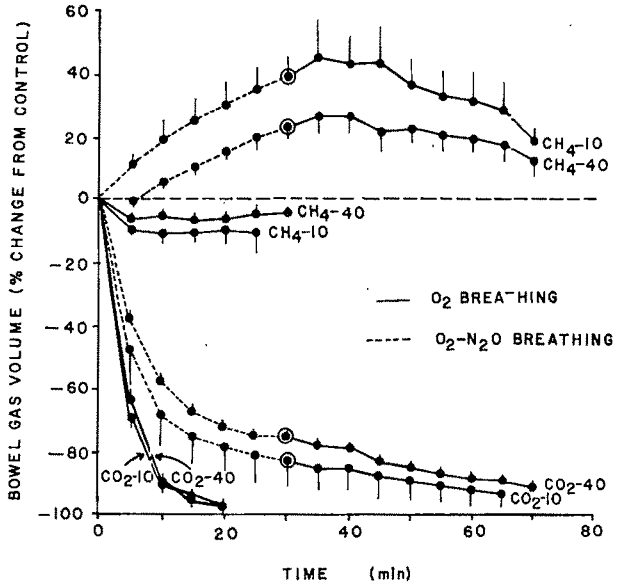

FIG 2. Effect of 100% O_2 (O_2) or 21% O_2-balanced N_2O (O_2-N_2O) breathing on bowel gas volume. Four bowel segments are represented each initially injected with 10 cc (ATPD) or 40 cc of methane (CH_4-10, CH_4-40) or carbon dioxide (CO_2-10, CO_2-40). The change over from O_2-N_2O to O_2 breathing at 30 minutes is emphasized by a circle (see text for details). The $\bar{X} \pm$ SE of the results from four dogs are given.

Discussion

Previous studies have shown that breathing N_2O causes the expansion of air injected into the lumen of the bowel.[3] Our results additionally suggest that breathing N_2O augments the accumulation of intestinal gases.

Methane, H_2, CO_2, and N_2 comprise the major constituents of bowel gas in a variety of terrestrial mammals including man. Methane, H_2, and CO_2 are produced by bacterial metabolism and acidification of bowel contents (CO_2) whereas swallowed air is the primary source of N_2. Gaseous distension of the bowel does not occur so long as absorption by blood or elimination as flatus keeps pace with production. Blood flow to the intestine may equal 1 L/min. Such a flow can absorb 15 ml/min of N_2 or H_2, 32 ml/min of CH_4, or 488 ml/min of CO_2 (Table 2). These absorption rates presume that no barrier to diffusion is present and that the gas in question exists at a 100% concentration in the gut. Elimination as flatus requires adequate intestinal motility. By decreasing motility, anesthesia and anesthetic adjuvants such as atropine

TABLE 1

Accumulated Bowel Segment Gas Volume in Halothane-Anesthetized Ponies Breathing Oxygen (O_2) or 30% Oxygen Balance Nitrous Oxide (O_2-N_2O)

Pony no.	Bowel segment gas volume (ATPD) while breathing		Increase in gas volume with O_2-N_2O breathing	Sampling time
	O_2	O_2-N_2O		
	ml		%	*min*
1	52	93	79	90
2	181	433	139	60
3	115	144	25	60
4	21	29	38	60
5	391	509	30	60
$\bar{X}$ ± SEM	152 ± 66	242 ± 96	62 ± 21	—

TABLE 2

Blood Solubility and Ratio of Diffusion Rate of Gases

Gas	Blood solubility (S) at 37–38 C		Ratio of diffusion rate (DR) of N_2O in blood to gas (DR_{N_2O}/DR_x)†
	S*	S_{N_2O}/S_x	
Nitrogen	0.0147[8]	31.7	25.29
Hydrogen	0.0149[9]	31.3	6.65
Methane	0.0320[9]	14.6	8.79
Carbon dioxide	0.488[8]	0.96	0.96
Nitrous oxide	0.466[8]	—	—

* Superscript figures are references.

† $DR_{N_2O}/DR_x = S_{N_2O}\sqrt{\text{mol wt}_x}/S_x\sqrt{\text{mol wt}_{N_2O}}$ (pressure gradient assumed equal).

may increase the importance of absorption to the prevention of intestinal gas accumulation.

Absorption itself may be compromised by the administration of nitrous oxide. While the bowel gas is leaving the segment, N_2O enters from the blood. In this case the relative rates of movement of the bowel gas and that of N_2O determine the volume history of the bowel segment. Nitrous oxide is a comparatively soluble gas and for a given partial pressure gradient the ratio of diffusion rate of N_2O to N_2, H_2, and CH_4 is great (Table 2). Thus, a rapid exchange of N_2O results. The N_2O entering the gut not only increases lumen volume but, by dilution, it also affects the partial pressure of the resident gas, alters its pressure gradient, and slows its efflux (Table 2 and Fig 2). Once the gut lumen contains N_2O, in addition to the resident bowel gas, the additional influx or efflux of either one must alter the pressure gradient of those remaining. Both this influx of nitrous oxide and the dilution effect may account for the intestinal distension reported to have developed during clinical anesthesia.[1, 2]

The discontinuation of N_2O does reverse the gas expansion seen with methane and accelerates the decay with CO_2 (Fig 2). However, the respective reversal and acceleration that we found took place slowly. The slowness may in part result from the time required to wash N_2O out of the lungs and intestinal tissue. In part, the slowness also may result from the more limited gradient forcing expulsion of N_2O: the N_2O is introduced at 79% of 1 atm, but elimination begins with a lower driving pressure from within the gut. Regardless of the cause, the clinical implication is obvious; distension brought about by N_2O breathing cannot be reversed in a few minutes.

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ANESTH ANALG
58:409-412, 1979

Serum Inorganic Fluoride Levels in Obese Patients during and after Enflurane Anesthesia

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BENTLEY, J. B., VAUGHAN, R. W., MILLER, M. S., CALKINS, J. M., AND GANDOLFI, A. J.: Serum inorganic fluoride levels during and after enflurane anesthesia. Anesth Analg 58:409–412, 1979.

Serum ionic fluoride levels in 24 markedly obese patients (127.6 ± 6.0 kg) and seven nonobese control subjects (67.3 ± 1.2 kg) were compared during and following enflurane anesthesia (<2.0 MAC hr). Peak serum fluoride levels were higher (28.0 ± 1.9 vs 17.3 ± 1.3 μM/L, $p < 0.01$) and the rate at which fluoride levels increased was more rapid (slope 5.6 vs 2.5 μM/L/hr) in obese patients than in control patients. No clinical evidence of nephrotoxicity was found in either group. Vasopressin resistance tests were not performed, and thus it is unknown whether subclinical nephrotoxicity occurred in either study group. Possible reasons for increased enflurane metabolism in obesity are discussed. These possibilities include differences in fluoride ion kinetics, hepatic delivery and penetration of volatile anesthetics, and altered hepatic microsomal enzyme activity. Obesity rather than weight is an important determinant of anesthetic biotransformation.

Key Words: ANESTHETICS, Volatile: enflurane; IONS: fluoride; COMPLICATIONS: obesity; BIOTRANSFORMATION (DRUG): enflurane.

IN 1973, Cousins and Mazze[1] correlated nephrotoxicity following methoxyflurane anesthesia with peak serum ionic fluoride levels. Renal toxicity increased as peak serum inorganic fluoride levels increased above 50 μM/L.[1] Subsequently Mazze et al demonstrated that subclinical nephrotoxicity occurred in volunteers receiving 9.6 MAC hours of enflurane anesthesia, despite peak serum fluoride levels of only 33.6 μM/L.[2] This suggests that duration of elevated serum ionic fluoride levels may be as important as peak levels in determining nephrotoxicity. In almost all previous studies investigating enflurane biotransformatin to ionic fluoride the patients were nonobese.[3-5] However, two markedly obese patients who had peak serum fluoride levels of 51 μM/L and 70 μM/L following enflurane anesthesia have been described.[2,5] The present study was designed to determine whether obese patients metabolize enflurane to inorganic fluoride ion to a greater extent than their nonobese counterparts.

Methods

Twenty-four markedly obese adult patients (127.6 ± 6 kg) and seven healthy nonobese control subjects undergoing elective abdominal surgery were studied. Approval for this study was obtained from the Human Subjects Committee at the University of Arizona Health Sciences Center, and prior consent was obtained from each patient. Preoperative serum electrolytes, urinalysis, and serum creatinine were within normal limits in all patients. No patient had a history

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of renal dysfunction, nor did present medication include drugs known to alter renal function. Premedication consisted of diazepam, 10 to 15 mg orally, and glycopyrrolate, 0.2 to 0.3 mg IM. Gallamine (20 mg) was given and the patients were preoxygenated (3 to 5 minutes) prior to induction of anesthesia. Anesthesia was induced with sodium thiopental (375 to 750 mg); this was followed by succinylcholine (100 to 160 mg), cricoid pressure, and placement of cuffed endotracheal tubes. Anesthesia was maintained for 2 hours with 50:50 nitrous oxide:oxygen and enflurane. Accuracy of the enflurane vaporizer had been previously verified by gas chromatographic calibration. Enflurane was discontinued after 2 hours. Subsequently anesthesia was maintained with fentanyl (0.10 to 0.30 mg) and 60:40 nitrous oxide:oxygen for the remainder of the operative procedure. Pancuronium bromide was employed for muscle relaxation while ventilation was controlled to maintain arterial carbon dioxide tension (Pa_{CO_2}) at 40 ± 5 torr. Arterial oxygen tension (Pa_{O_2}) remained between 80 and 130 torr. Arterial blood gas values were confirmed by serial determinations. End-tidal enflurane was measured by Beckman LB-2 infrared gas analyzer sampling at a rate of 500 ml/min and/or by gas chromatography. MAC hours were calculated as previously described.[1, 2]

Arterial and/or venous blood samples were obtained prior to enflurane administration and at 30-minute intervals throughout the operative period. Thereafter, samples were taken 3, 4, 6, 8, 12, 18, 24, and 48 hours following initiation of anesthesia. An Orion fluoride ion-specific electrode was used to determine serum inorganic fluoride concentrations.[2]

All urine was collected intraoperatively and for 48 hours postoperatively. Diuretics were not administered either intra- or postoperatively. The statistical significance of intergroup variations in the mean serum ionic fluoride during and following anesthesia was determined by using paired-*t* tests for statistical analysis; $p < 0.05$ was considered significant.

TABLE 1

Vital Statistics and Treatment Data (mean ± SE)

	Obese	Nonobese
n	24	7
Ht (cm)	165.9 ± 0.9	167.0 ± 2.0
Wt (kg)	127.6 ± 6.0	67.3 ± 1.2
Body mass index (kg/m²)	45.9 ± 1.7	23.6 ± 2.0
Age (yr)	37.7 ± 5.1	52.3 ± 5.1
MAC (hr)	1.8 ± 0.2	1.9 ± 0.2

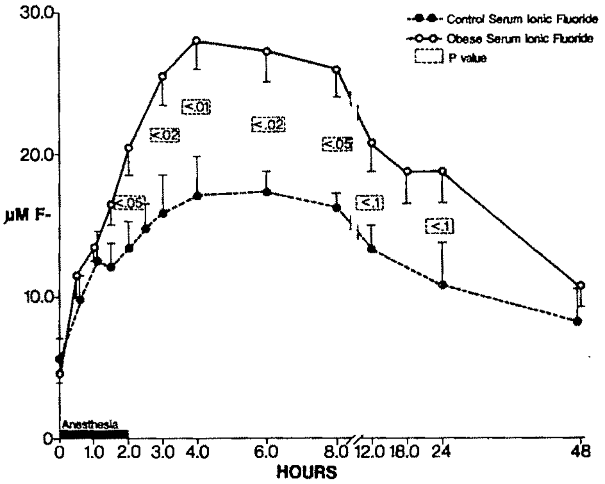

FIG 1. Serum ionic fluoride concentrations (µM) during and following 2 hours of enflurane anesthesia in 24 obese and seven nonobese patients (mean ± SE).

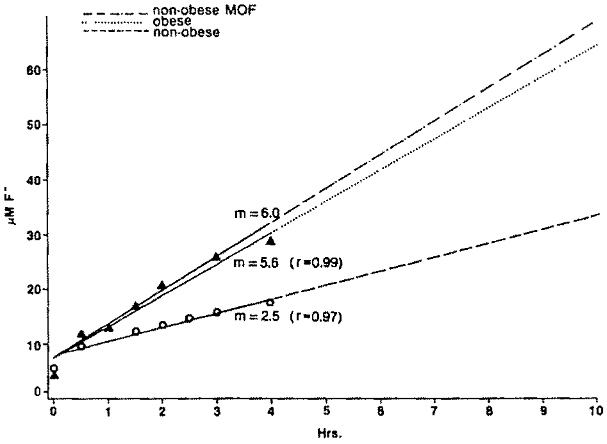

FIG 2. Linear regression analysis of mean serum ionic fluoride concentrations with time. Obese (n = 24) and nonobese (n = 7) patients were monitored for serum ionic fluoride during and following 2 hours of enflurane anesthesia until peak concentrations were reached. $m = \Delta F^-/\text{hour}$; broken lines represent extrapolations. Nonobese MOF line produced from Creasser C, Stoelting RK: Anesthesiology 39:537, 1973.

Results

Preoperatively no significant variation between obese and nonobese patients' groups was detected with the exception of weight and age (Table 1). Enflurane exposure in the obese and nonobese groups averaged 1.8 ± 0.2 and 1.9 ± 0.2 MAC hours, respectively. Despite similar enflurane exposures mean peak serum fluoride levels were significantly higher during and after anesthesia in obese patients (28.0 ± 1.9 µM/L) than in control patients (17.3 ± 1.3 µM/L) (Fig 1). A linear increase in ionic fluoride with time was found in both groups of patients intraoperatively. This linear increase continued postoperatively until peak fluoride levels were reached. The latter peak occurred 4 hours after induction of anesthesia (i.e., 2 hours after discontinuing enflurane) in both groups of patients (Fig 1). In addition, the rate of rise of ionic fluoride in obese patients (Fig 2) was more than twice that in nonobese counterparts (5.6 vs 2.5 μM/L/hr). Furthermore, after 24 hours, fluoride levels remained higher in obese patients (18.8 ± 2.3 μM/L) than in nonobese patients (10.7 ± 3.1 μM/L) (Fig 1). Noteworthy in obese patients was the extensive intragroup variability in serum ionic fluoride levels (Fig 3).

Postoperative serum electrolyte and creatinine values in both groups of patients demonstrated no significant difference from preoperative values (Table 2). Urine output in the two groups was not significantly different. There was no correlation between weight and peak serum ionic fluoride, nor was there a correlation between body mass index (weight (kg)/height (m^2)) and serum ionic fluoride.[6]

Discussion

In the present study peak serum inorganic fluoride levels averaging 28 ± 1.9 uM/L in the obese patients occurred 2 hours after cessation of enflurane administration. This was significantly greater ($p < 0.01$) than peak levels observed in our nonobese patients and approaches levels found after 9.6 MAC hours in nonobese volunteers.[2] Also, serum ionic fluoride levels in obese patients increased more rapidly and remained elevated slightly longer than in nonobese patients. The rate of rise of ionic fluoride in obese patients was similar to that reported to occur in nonobese patients during methoxyflurane administration (i.e., 6 μM/L, Fig 2).[7] These data support the premise that increased enflurane biotransformation occurs in markedly obese patients. The mechanism of altered serum fluoride in obese patients cannot be determined from the present data. However, differences in fluoride ion kinetics, hepatic delivery and penetration of volatile anesthetics, or hepatic microsomal enzyme activity in obese patients may explain the observed increase in levels of fluoride ion.

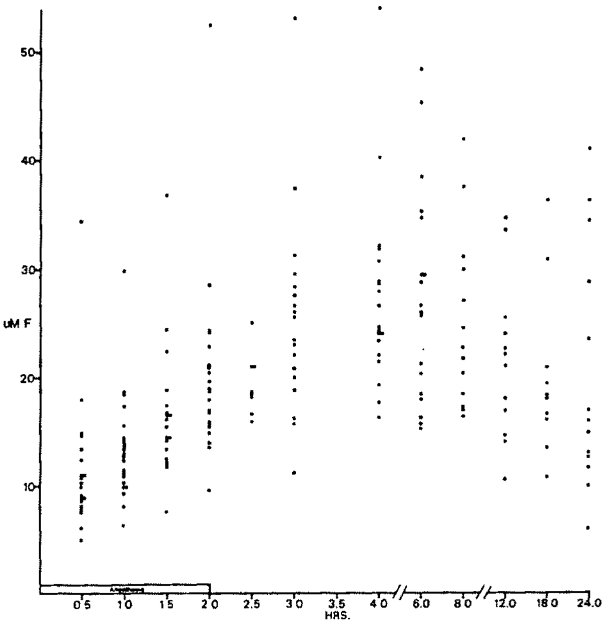

FIG 3. Serum ionic fluoride concentrations (μM) in 24 obese patients during and following 2 hours of enflurane anesthesia.

Marked variability in enflurane metabolism in both obese and nonobese patients has been previously reported[1–3, 5] and probably partially reflects biologic variation. Whether obese patients have increased hepatic microsomal enzyme activity is not known. None of our patients were taking medications known to increase microsomal enzyme activity. Other factors that influence microsomal enzyme activity include age, gender, diet, and smoking habits.[8] Sex distribution and smoking habits were similar in both groups of patients. Diet was not controlled. Differences in this variable could lead to altered enzyme activity, thus influencing anesthetic metabolism. Age was dissimilar in the two groups. However, when the age variable was controlled using multiple regression analysis, fluoride levels in the obese and nonobese patients were still significantly different ($p < 0.002$).

Fatty infiltration of the liver is known to occur in more than 80% of obese patients.[9] Increased hepatic lipid could lead to increased uptake of a lipid-soluble anesthetic such as enflurane by the liver.[10] This increased anesthetic exposure to the hepatic microsomal

TABLE 2

Preoperative and Postoperative Serum Values (mean ± SE)

	Na$^+$	K$^+$	Cl$^-$	HCO$_3^-$	Creatinine
			mM/L		*mg/dl*
Obese (n = 20)					
Preoperative	141.0 ± 0.6	4.0 ± 0.1	104.0 ± 0.7	27.6 ± 0.5	0.86 ± 0.04
Postoperative day 1	138.1 ± 0.6	4.1 ± 0.1	104.5 ± 0.8	23.6 ± 1.3	0.81 ± 0.04
Nonobese (n = 7)					
Preoperative	140.1 ± 1.6	4.1 ± 0.2	105.6 ± 0.2	25.6 ± 1.1	0.95 ± 0.08
Postoperative day 1	139.0 ± 1.0	4.5 ± 0.3	105.5 ± 1.3	24.3 ± 1.7	0.87 ± 0.14

enzyme systems may result in increased anesthetic biotransformation.

Differences in cardiac output and distribution of cardiac output between the two groups may also explain differences in enflurane metabolism. Obesity indirectly increases cardiac output and redistributes it to adipose tissue.[11] This occurs despite a decrease of tissue blood flow to fat (milliliters per gram of tissue) in obesity.[12] Fat has a large capacity for anesthetic storage and may serve as a reservoir to provide continued delivery of drug to the liver for metabolism. This may explain the prolonged elevation of ionic fluoride levels in our obese patients following termination of anesthesia. In addition, unanesthetized obese patients have greater splanchnic blood flows than do nonobese patients.[11] A greater fraction of administered enflurane may thus be exposed to the liver for subsequent biotransformation.

Whether fluoride ion kinetics are similar in obese and nonobese patients is not known. Obese patients do have increased cortical bone mass compared to nonobese subjects.[13] This could cause lower serum ionic fluoride levels since 50% of serum fluoride may be absorbed into bone.[14] Also, renal excretion of fluoride might have been different in the two groups. Obese patients may have an associated protein-losing nephropathy[15] which may produce increased urinary fluoride excretion. However, none of our patients had preoperative proteinuria. In addition, renal function is not an important determinant of peak ionic fluoride levels.[14] Moreover, previous data indicate similar renal excretion of ionic fluoride ion in obese and nonobese patients.[7, 10]

Whether subclinical renal dysfunction occurred was not determined in either group. No change from preoperative values in serum electrolytes or creatinine was detected postoperatively in either group, and urine output in the two groups was similar. A more specific test of urine concentrating ability (vasopressin resistance) was not performed. However, peak serum fluoride ion and duration of elevated fluoride values were similar to those previously reported to cause impairment of the urine concentrating mechanism.[1] Thus, subclinical nephrotoxicity may have occurred in the obese group. Also, our interpretation of the results of previous studies in nonobese patients[2, 4] indicates that serum fluoride ion concentrations will increase to peak values in a linear manner following up to 8 hours of enflurane anesthesia. If the linear increase in fluoride ion found in our obese patients (5.6 M/L/hr) continues during prolonged exposure to enflurane as in nonobese patients, clinical nephrotoxicity might occur (Fig 2). The data in this study neither support nor deny these possibilities.

The lack of correlation between serum ionic fluoride and either weight or body mass index is not surprising. As discussed previously, many physiologic and pathologic changes that occur in obesity may increase anesthetic metabolism. These changes are probably not directly related to increasing weight. A correlation between weight and ionic fluoride would not be expected. Thus, although this study indicates that while obesity is a determinant of biotransformation of enflurane, the degree of obesity cannot be used to predict postanesthetic serum fluoride levels.

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REVIEW

article

Drug Interactions and Anesthesia: A Review

Bruce F. Cullen, MD,* and Malcolm G. Miller, MD†

THE AVERAGE patient may receive eight different drugs during a hospitalization[42,46] and an additional five to 10 drugs during anesthesia. A knowledge of the possible interactions between these drugs is essential for the safe conduct of anesthesia. Although several reviews on this subject have appeared,[10,16,29,61] the introduction of new drugs and the realization of previously unrecognized interactions makes an updated discussion necessary. The intent of this article is not to be a comprehensive survey of all drug interactions, but rather a useful review of common drugs and problems for the practicing clinician.

Mechanisms of Drug Interactions

Physical or Chemical Incompatibility

Many drugs are incompatible when mixed in the same solution. For example, when narcotics, such as meperidine (pH 3.5), are mixed with barbiturates, such as thiopental (pH 10.8), a precipitate may form. A precipitate may also form when pancuronium and thiopental are administered simultaneously into an intravenous tubing. The precipitation is the result of the change in pH.

Physical drug interaction can also occur in vivo. A common example is the neutralization of heparin with protamine. Protamine is a base that combines with the strongly acidic heparin molecule to form a stable salt with no anticoagulant activity.[19]

Interaction at Site of Absorption

Frequently the presence of one drug may alter the uptake or absorption of another. A common example is the addition of epinephrine to a local anesthetic. The vasoconstricting action of epinephrine will delay the uptake of the local anesthetic into the circulation and prolong the block as well as decrease the incidence of toxicity.

Inhalation anesthetics may also interact with one another to alter the rate of uptake in the alveolus. An example of this is the "second gas effect" whereby the addition of nitrous oxide to an inspired mixture accelerates the rate of rise of the alveolar concentration of another anesthetic, such as halothane, which is administered simultaneously (Fig 1). The second gas effect has been explained on the basis of a concentrating action and an increase in alveolar ventilation, which are both secondary to the uptake of large volumes of nitrous oxide into the blood.[71]

Altered Protein Binding

Many drugs bind to plasma proteins, and in that state they are pharmacologically inactive since only the unbound or free fraction of the drug is available to combine with tissue receptor sites.[20(p 692)] If there is competition between two drugs for the same binding

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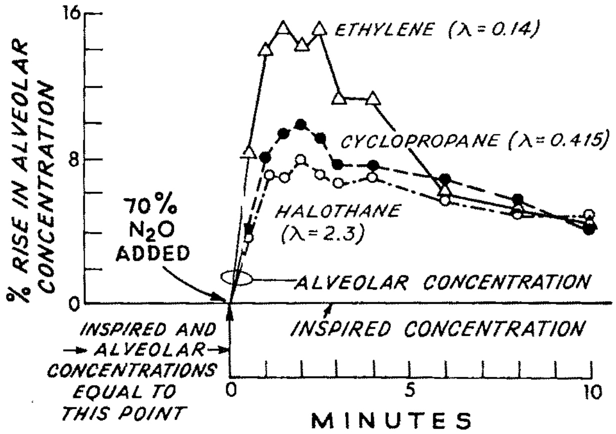

FIG 1. Percent rise in alveolar concentration of ethylene, cyclopropane, and halothane following the addition of 70% nitrous oxide to the inspired mixture. The inspired concentration of the three anesthetics was held constant after the introduction of nitrous oxide.[71]

sites on plasma proteins, unexpected results may occur when the drugs are administered simultaneously.

For example, barbiturates that readily bind to proteins can be displaced by x-ray contrast media. The injection of contrast media releases barbiturates from proteins and deepens the level of anesthesia. This has been confirmed experimentally by demonstrating a prolongation of barbiturate anesthesia in rats after injection of x-ray contrast media.[38] A prolongation of succinylcholine paralysis in the presence of local anesthetics has also been attributed to competition at plasma protein binding sites,[75] although the validity of this explanation has been questioned.[16]

Competition for Receptor Sites

It is possible for two drugs to compete for a single receptor. The action of one drug may thus be altered by the administration of another, an interaction which is assumed to follow the law of mass action.

A common example of this phenomenon is the competitive interaction of *d*-tubocurarine and acetylcholine at receptor sites in the myoneural junction. To reverse a *d*-tubocurarine block, an anticholinesterase, such as neostigmine, is given, which results in an increased level of acetylcholine and a displacement of curare molecules from receptor sites.

Altered Metabolism

There are many instances where the administration of one drug alters the metabolism of another and possibly changes the action of both. Some drugs stimulate proliferation of smooth endoplasmic reticulum in liver cells so that metabolism of other drugs is enhanced. Agents thought to be capable of inducing drug-metabolizing enzymes include alcohol, coffee, tea, barbiturates, inhalation anesthetics, narcotics, phenylhydantoin, and many tranquilizers.

As an example of the problems that may arise from this type of interaction, the administration of enzyme-inducing drugs can alter the required doses of anticoagulants. Severe bleeding has been reported in patients who are taking anticoagulants and who abruptly discontinue intake of an enzyme-inducing drug, such as phenobarbital. Cessation of phenobarbital treatment results in a concomitant reduction in the rate of anticoagulant metabolism, and a given dose of anticoagulant will have an exaggerated effect. Several weeks may be required for this process.[35]

Enzyme induction may also play a role in halothane-related hepatic dysfunction. Some investigators have developed an animal model of "halothane-hepatitis," which is apparent when mice are given both halothane and phenobarbital in a hypoxic environment.[5, 78] Enzyme induction with phenobarbital is necessary to produce the lesion. The proposed mechanism involves conversion of halothane metabolism from a normal, oxidative pathway to an abnormal, reductive pathway.

Enzyme induction should also be of concern when administering methoxyflurane, since it is metabolized to liberate nephrotoxic free fluoride ion. It would be unwise to administer high doses of methoxyflurane to a patient who is also taking a drug such as phenobarbital since metabolism of methoxyflurane is enhanced, and toxic levels of fluoride ions may be released.[43] Enflurane may also be metabolized to produce free fluoride; however, the rate of metabolism and the risk of nephrotoxicity does not increase if patients are taking enzyme-inducing drugs. Dooley et al[14] measured serum fluoride levels in 102 surgical patients who were taking enzyme-inducing drugs, such as ethanol, phenytoin, and phenobarbital. No significantly increased serum fluoride levels or renal damage were observed in these patients given enflurane anesthesia. The reason for this observation is not clear, although the low solubility of enflurane in blood and tissues may prevent high concentrations of the anesthetic from being delivered to hepatic enzymes.

A drug may inhibit enzymes that are responsible for metabolism of other drugs. This occurs when patients treated with echothiopate (phosphaline iodide) are given succinylcholine.[55] Echothiopate, an anticholinesterase useful in the treatment of glaucoma, depletes plasma pseudocholinesterase and thus prolongs the action of succinylcholine.

Altered Excretion

It is possible for the administration of one drug to alter the excretion of another. An example is the increased excretion of phenobarbital that follows alkalinization of the urine. Phenobarbital is a base that is poorly excreted in acid urine. The administration of bicarbonate hastens its elimination and thus has been utilized in treating patients with phenobarbital overdose.[37]

A second type of interaction at the site of excretion is the effect of narcotics on the rate of recovery from inhalation anesthesia. Inhalation anesthetics are excreted mainly via the lungs, a process which depends upon adequate alveolar ventilation. If ventilation is depressed by narcotics, excretion of the inhalation anesthetics is delayed and anesthesia prolonged.

Specific Drug Interactions

Antihypertensive Drugs

Many drugs are used to treat hypertension, and they act by a variety of mechanisms. One group, exemplified by reserpine, acts by depleting catecholamine stores. Shortly after this drug was introduced into clinical use, a concern spread among anesthesiologists because patients who were taking it often experienced severe hypotension and bradycardia when anesthetized.[8, 79] The hypotension was often difficult to treat. It was postulated that the depletion of catecholamine stores rendered these patients particularly sensitive to the depressant cardiovascular effects of anesthetic agents. Many anesthesiologists adopted a rule that reserpine and other catecholamine-depleting drugs should be discontinued 2 weeks prior to surgery and anesthesia.

The validity of this dictum has since been questioned, and it is now generally considered that antihypertensive therapy should not be withdrawn prior to anesthesia.[18, 51] Prys-Roberts et al[60] analyzed the cardiovascular responses of treated and untreated hypertensive patients during anesthesia and concluded that although a reduction of blood pressure is common when hypertensive patients are anesthetized, a more serious risk exists for those patients whose hypertension is untreated.

Some antihypertensive drugs may also affect anesthetic requirements. After observing that patients receiving alphamethyldopa required less anesthesia, Miller and colleagues[44] demonstrated a reduction of halothane MAC when animals were treated with alphamethyldopa or reserpine. These drugs not only act peripherally, but centrally as well because they can cross the blood-brain barrier. Guanethidine, in contrast, did not reduce anesthetic requirements, presumably because the drug does not cross the blood-brain barrier. Miller et al[44] postulated that the reduction of MAC with reserpine therapy was due to depletion of central catecholamine stores because of an observed increased anesthetic requirement when animals were treated with iproniazid, a drug which increases central nervous system catecholamines.

The thiazide diuretics are another class of antihypertensive drugs that can present problems for the anesthesiologist, since patients taking these drugs commonly have a low serum potassium. A low serum potassium can increase the possibility of arrhythmias,[9] increase the toxicity of drugs (such as digitalis),[40] and alter the action of nondepolarizing muscle relaxants.[22] Patients treated with diuretics may also develop a decreased blood volume and thus may be at an increased risk for hypotension during anesthesia.

Clonidine is a relatively new antihypertensive drug that acts by inhibiting bulbar sympathetic centers. It has a relatively short half-life (less than 12 hours), and its acute withdrawal may result in severe rebound hypertension.[28] Patients should be maintained on this drug up to and including the morning of surgery. Failure of the patient to take the usual morning dose of clonidine may result in severe intraoperative or postoperative hypertension.[3, 7] If the surgical procedure precludes use of oral medications for a few days, an antihypertensive agent which can be used parenterally should be substituted for the oral clonidine starting a few days preoperatively.

Beta-Adrenergic Blockers

Beta-adrenergic blockade with drugs such as propranolol is used in the treatment of a number of diseases which include angina pectoris, hypertension, cardiac arrhythmias, thyrotoxicosis, and pheochromocytoma. The interaction of beta-adrenergic blockade and inhalational anesthetic agents on cardiovascular function has been studied in closed-chest dogs chronically implanted with cardiovascular flow- and pressure-measuring instruments. Pretreatment of the dogs for 3 weeks with propranolol, 20 mg/kg/day, results in a small degree of additional cardiac depression at inspired concentrations of 1.0% and 2.5%

halothane with intermittent positive pressure ventilation and normocapnia.[62] No adverse hemodynamic effects occur with the combination of propranolol, halothane, and hypoxemia.[63] Beta-blocked dogs anesthetized with halothane tolerate hemorrhage as well as dogs that are not beta-blocked, but the combination of propranolol and trichloroethylene markedly reduces cardiac output during hypovolemia, and cardiovascular function does not return to normal after restoration of the circulating blood volume. Therefore, the use of trichloroethylene in the presence of propranolol may not be advisable.[64]

The administration of 0.3 mg/kg of propranolol to dogs anesthetized with 2% enflurane reduces mean arterial pressure by 11%, and the rate of rise of maximum left ventricular pressure (max LV dP/dt) by 17%, but does not cause significant changes of heart rate, cardiac output, left ventricular minute work, or systemic vascular resistance. After propranolol, 3% enflurance reduces mean arterial pressure by 25%, LV dP/dt by 26%, cardiac output by 39%, and left ventricular minute work by 51%, and increases systemic vascular resistance by 48%.[26] Isoflurane causes less myocardial depression and impairment of cardiac function than either enflurane and halothane, and beta-receptor blockade induced with propranolol produces no serious interaction with isoflurane.[25]

The administration of practolol, 2 mg/kg, to dogs anesthetized with 0.4% methoxyflurane causes profound reductions in cardiac output and the indices of myocardial contractility. Three of 10 dogs died from low cardiac output states within 15 minutes after the administration of practolol.[65] This unexpected adverse interaction of methoxyflurane and beta-blockade may in part explain the death, reported by Viljoen et al,[76] of four of five cardiac surgical patients who had been treated with propranolol and anesthetized with methoxyflurane.

Patients treated with propranolol can be safely anesthetized for both cardiac and noncardiac operations.[32, 33] In fact, patients treated with propranolol for angina pectoris may sustain myocardial infarction if the drug is acutely withdrawn.[13, 47] Thus, if propranolol is required for medical control of the patient's symptoms, it is probably unwise to discontinue medication before surgery unless methoxyflurane is to be used. The administration of propranolol does not alter the minimum alveolar concentration of halothane in dogs.[74]

Antiarrhythmic Drugs

Lidocaine, a frequently used antiarrhythmic drug, can be used to induce and maintain general anesthesia. In the presence of 70% nitrous oxide in oxygen, a constant intravenous infusion of lidocaine, 45 to 100 μg/kg/min, for 4 to 5 minutes, induces unconsciousness, and 2 to 2.5 mg/kg given intravenously in divided doses over the next 5 minutes maintains surgical levels of anesthesia. Thus, it is not surprising that plasma lidocaine concentrations of 3.0 to 11.6 μg/ml decrease the anesthetic requirements of halothane in dogs approximately 10 to 28%.[23]

Arrhythmias during anesthesia are commonly attributed to suppression of primary pacemaker foci with enhancement of automaticity at ectopic foci.[75] Lidocaine and diphenylhydantoin are effective in the treatment of these arrhythmias. Lidocaine is more effective for ventricular arrhythmias secondary to an increase in catecholamines and diphenylhydantoin for arrhythmias due to digitalis toxicity. However, disturbed conduction may contribute to the production of arrhythmias as a result of reentry of excitation. Halothane impairs atrioventricular conduction as evaluated by His-bundle electrocardiography in dogs. Both lidocaine and diphenylhydantoin further depress atrioventricular conduction, with lidocaine causing greater depression of conduction than diphenylhydantoin. Thus, these drugs may be ineffective in treatment of arrhythmias due to the disturbances in conduction during halothane anesthesia.[2]

The action of neuromuscular blocking agents is enhanced by quinidine, procaine, and lidocaine.[34, 45] Muscle relaxants (*d*-tubocurarine, pancuronium, and succinylcholine) and local anesthetics (cocaine, procaine, lidocaine, etidocaine, and procaine methobromide) increase the neuromuscular blocking effects of each other in the rat's phrenic nerve-hemidiaphragm preparation. The combined neuromuscular effects of the two types of compounds are greater than that expected from summation of the effects of the individual compounds, and thus probably represent true potentiation.[41]

Digitalis Glycosides

Digitalis preparations are useful in the treatment of congestive heart failure and supraventricular arrhythmias. However, they have a relatively limited margin of safety. Also, serum potassium concentrations are pH-dependent and change with variations of the arterial carbon dioxide tension. Serum potassium decreases with hyperventilation, and the likelihood of digitalis toxicity increases.[40]

Halothane reduces the cardiotoxicity of the digitalis compounds[50] and is effective in the treatment of ouabain-induced ventricular tachycardia in intact dogs.[39, 59] Hence, an adequate dose of digitalis in the awake patient may become inadequate during halothane anesthesia. Conversely, a dose of digitalis given during halothane anesthesia may become excessive once the patient awakens.

The question of whether to prophylactically digitalize the elderly patient or one with marginal cardiac disease has not been fully answered. Deutsch and Dalen[11] advocated prophylactic digitalization on the basis that digitalis may prevent or minimize the myocardial depressant effects of anesthetics. Furthermore, digitalis, by virtue of its positive inotropic effect, would facilitate any necessary increase in cardiac output during the operation. In contrast, Strong and Keats argued against prophylactic digitalization since intraoperative digitalis toxicity is difficult to diagnose and treat.[73]

Epinephrine

Epinephrine is often used to reduce bleeding during certain surgical procedures. The dose of epinephrine which provokes ventricular irritability varies with the different halogenated anesthetics and with the amount of concurrent lidocaine administration. The dose of epinephrine that causes premature ventricular contractions in 50% of patients, i.e., the ED_{50}, is 2.1 μg/kg with halothane, 6.7 μg/kg with isoflurane, and 10.9 μg/kg with enflurane (Fig 2).[30] Arrhythmias always occur during or within 2 minutes after injection. These observations hold true for anesthetic gas tensions of 1.25 times the minimum alveolar concentration for each of the three anesthetics. No ventricular arrhythmias are seen when less than 1.8 μg/kg of epinephrine is injected submucosally during halothane anesthesia, and when less than 5.4 μg/kg is used during isoflurane anesthesia.[30] A 1:200,000 solution contains 5 μg/ml of epinephrine.

Although the ED_{50} of epinephrine during enflurane anesthesia is higher than during halothane and isoflurane anesthesia, viz, 10.9 μg/kg during enflurane as opposed to 2.1 μg/kg and 6.7 μg/kg during halothane and isoflurane anesthesia, respectively, ventricular arrhythmias can occur with epinephrine doses as low as 3.6 μg/kg during enflurane anesthesia. In other words, the ratio between the lowest dose producing arrhythmias and the ED_{50} was smaller for enflurane than for halothane or isoflurane. There thus seems to be a qualitative as well as a quantitative difference in the interaction of epinephrine with enflurane as compared to halothane and isoflurane. During enflurane anesthesia patients are more likely to have ventricular arrhythmias if the maximum systolic blood pressure is greater than 160 mm Hg.[27]

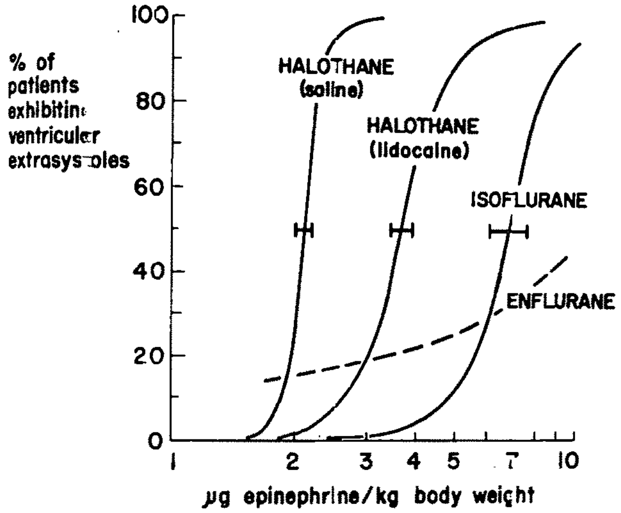

FIG 2. Interaction of epinephrine with 1.25 MAC halothane, isoflurane, and enflurane. The addition of 0.5% lidocaine to the epinephrine solution shifts the halothane dose-response curve to the right. The slope of the enflurane dose-response curve suggests a qualitative as well as a quantitative difference in the interaction of epinephrine with enflurane as compared to halothane and isoflurane.[30]

An increase of the concentration of lidocaine in the epinephrine solution from 0 to 0.5 to 1.0% increases the minimum dose of epinephrine which causes ventricular arrhythmias during enflurane anesthesia from 1.3 to 2.5 to 4.9 μg/kg.[27] During halothane anesthesia, the administration of 0.5% lidocaine with the epinephrine increases the dose of epinephrine which causes ventricular irritability by about 50%.[30] If ventricular arrhythmias do occur as a result of epinephrine injection, treatment with intravenous lidocaine is effective. Intravenous propranolol is indicated in the event of a persistent tachycardia.

Alcohol

Clinical observations suggest that acute alcoholic intoxication causes a reduction in anesthetic dose requirements and that sobered chronic alcoholic patients have a higher anesthetic dose requirement. A study on the effects of acute and chronic ethanol administration on isoflurane requirement in mice supports these observations. The intraperitoneal injection of 2 and 4 g/kg of ethanol reduces isoflurane ED_{50} to 1.23% and 0.38%, respectively (Fig 3). Isoflurane ED_{50} in sober mice, which is the mean dose at which 50% of the animals have no muscular response to the application of a tail clamp, is 1.33%.[31]

The isoflurane ED_{50} of chronically alcoholic mice

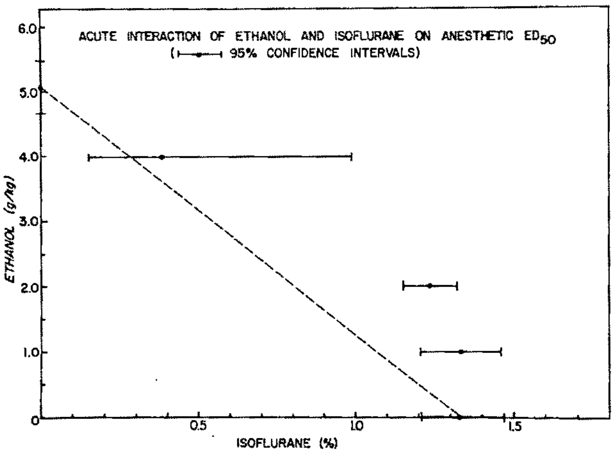

FIG 3. Acute interaction of 0, 1, 2, and 4 g/kg of ethanol on the isoflurane concentrations required to anesthetize 50% of mice. Pretreatment with 2 and 4 g/kg of ethanol reduces the isoflurane ED_{50} to 1.23 (1.15 to 1.32) and 0.38 (0.15 to 0.98), respectively.[31]

is 1.54% after 10 days of continuous alcohol ingestion and 1.69% after 20 days of alcohol ingestion. These mice had as their sole source of fluid 10% alcohol with 5% dextrose and had been allowed to sober up for 18 hours. The anesthetic tolerance acquired by these alcoholic mice persisted for 55 days after discontinuing alcohol ingestion; 55 days represent 6% of a mouse's life expectancy[31] (Fig 4).

Disulfiram

Disulfiram (Antabuse) is a drug administered to alcoholics to discourage them from further intake of alcohol. It acts by blocking oxidation of acetaldehyde and thus allows the ethanol metabolite to accumulate in toxic amounts. If patients who are taking disulfiram ingest alcohol, they experience severe nausea and vomiting.

The interaction of disulfiram with anesthetics has been reviewed[49] with the conclusion that no serious problems should occur provided no anesthetics are used that can be biotransformed to acetaldehyde. Should treatment with disulfiram be discontinued, it may require up to 2 weeks for total elimination from the body.

Anticoagulants

There is no evidence that general anesthesia is a particular hazard when patients are taking anticoagulants. Regional anesthesia, in contrast, is relatively contraindicated for patients taking anticoagulants, although some anesthesiologists will administer spinal anesthesia to patients with a modestly elevated prothrombin time. This problem has been made more frequent by the introduction of low-dose heparin therapy for prevention of deep vein thrombosis in surgical patients.[54] The safety of administering regional anesthesia to patients receiving low-dose heparin (for example, 5,000 units every 12 hours) has not yet been demonstrated. The activated coagulation time (ACT) can be determined quite easily in the operating room to check the degree of anticoagulation of patients on low-dose heparin.

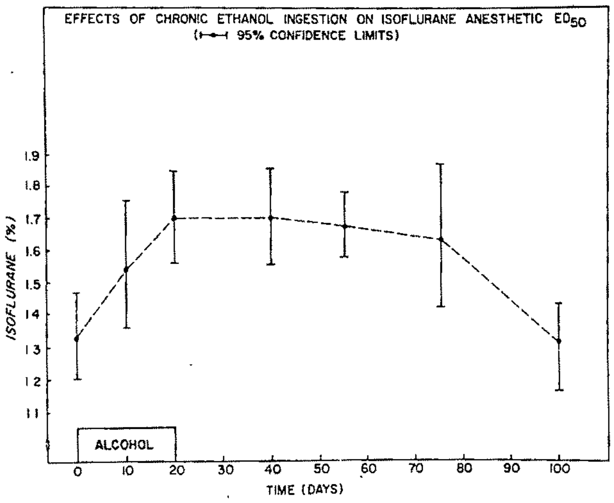

FIG 4. Effects of chronic ethanol ingestion on isoflurane requirement in mice. The isoflurane ED_{50} is 1.54 after 10 days and 1.69 after 20 days of alcohol ingestion. The effects persist for 55 days (or 6% of mouse life expectancy) after discontinuing alcohol ingestion.[31]

Antibiotics

Many of the common antibiotics potentiate the neuromuscular blocking effect of muscle relaxants, probably by binding calcium at the neuromuscular junction and by interfering with the release of acetylcholine. Patients who are receiving "mycin-type" antibiotics may be particularly sensitive to normal doses of non-depolarizing muscle relaxants.[1]

The action of muscle relaxants can also be influenced by anesthetic agents. Dose requirements for muscle relaxants are moderately reduced in the presence of halothane anesthesia and are lowest in the presence of enflurane or isoflurane anesthesia (Fig 5).[1]

Lithium

Lithium salts have been advocated in the treatment of alcoholism, manic-depressive psychoses, and other mental disorders. Lithium prolongs the duration of neuromuscular blockade produced by succinylcholine, decamethonium, and pancuronium, but has no effect on the duration of blockade by *d*-tubocurarine and gallamine. Lithium also prolongs the reversal time of pancuronium by prostigmine. The mechanisms for these interactions are complex. Chronic lithium therapy has no effect on plasma pseudocholinesterase activity. The potentiating effect of lithium on the duration of blockade produced by succinylcholine and decamethonium is explicable on the basis of reduced acetylcholine synthesis or release. The mechanism of interaction of lithium with pancuronium but not with *d*-tubocurarine or gallamine is not fully understood.[21]

The central nervous system effects of lithium suggest that it may also interact with general anesthesia. A study by Diamond et al[12] demonstrated that lithium significantly increased the duration of pentobarbital narcosis. This subject has not been studied in man.

Adrenal Steroids

Many patients come to surgery receiving steroids or having received them in the recent past. Whether or not to provide additional steroid intraoperatively is a question that has sparked much controversy. Prolonged therapy with steroids inhibits normal synthesis by the adrenal glands and thus causes functional adrenal insufficiency. Following termination of therapy with steroids, the pituitary-adrenal axis may take 9 to 10 months to recover.[56] An increased output of adrenal steroids normally occurs during anesthesia[53, 77] and surgical procedures,[4] but patients with iatrogenic adrenal insufficiency may not be able to cope with this added stress.

Plumpton et al[57, 58] investigated steroid "coverage" during surgery and found that patients who had stopped steroid treatment prior to surgery had a rise in plasma cortisol level during surgery which was indistinguishable from that occuring in normal patients and, furthermore, that 13 of 20 patients currently on steroid treatment also had a definite increase in plasma cortisol levels during surgery. No clear relationship between dosage or duration of therapy and ability to respond could be demonstrated. They suggested that cardiovascular collapse from adrenal insufficiency is unlikely to occur when therapy is terminated more than 2 months before the operation.

Kohler[36] reviewed the literature and determined that all patients with depressed hypothalamic-pituitary-adrenocortical function (whatever the cause) should receive 25 mg of cortisol intravenously during induction of anesthesia. Following major surgery, 100 mg of cortisol should be infused every 24 hours until normal oral intake can be resumed. No additional supplementation was recommended following minor surgery.

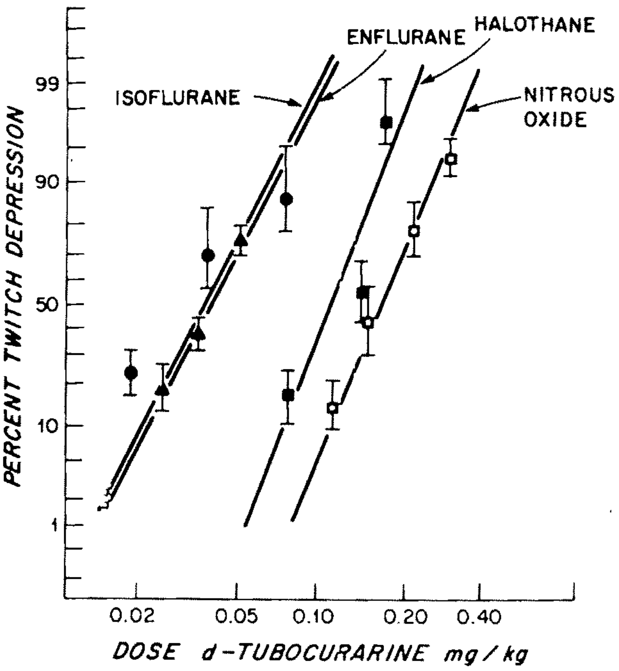

FIG 5. Interaction of *d*-tubocurarine with 66% nitrous oxide (open squares) and 1.25 MAC halothane (solid squares), isoflurane (circles), and enflurane (triangles). Potent volatile anesthetics reduce the dose requirement for the non-depolarizing relaxant and shift the dose-response curve to the left.[1]

Levodopa

Parkinson's disease is thought to be caused by a deficiency of dopamine in the basal ganglia and can be effectively treated with levodopa.[52] Levodopa crosses the blood-brain barrier and is converted to dopamine in the brain; but in the rest of the body, the drug circulates unchanged. The major systemic toxicity of levodopa involves the cardiovascular system and may include cardiac stimulation, peripheral vasoconstriction, and vasodilation of renal and mesenteric vessels. The cardiovascular effects of levodopa are complex; clinical doses (1 to 2 g), however, do not usually affect blood pressure or heart rate. Because levodopa has a short duration of action, therapy should be continued until the night before the operation and resumed as soon as possible postoperatively to prevent a recurrence of symptoms.

A major concern for the anesthesiologist should be the cardiovascular interaction of levodopa with anesthetic agents. Significant blood pressure alterations and arrhythmias may occur if the patient is anesthetized with halothane or cyclopropane.[18] In addition, because butyrophenone derivatives antagonize the action of dopamine, the use of haloperidol or droperidol is not recommended.[52] Fortunately these interactions are only seen if anesthesia is administered within 4 hours of levodopa administration since its half-life is so short.

Tricyclic Antidepressants

The tricyclic antidepressants, such as imipramine and amitriptyline, are commonly used to treat emotionally depressed patients. These drugs may cause cardiovascular instability and cardiac arrhythmias by blocking norepinephrine re-uptake into adrenergic nerve terminals and increasing norepinephrine concentrations in the circulation.[24] These patients may have arrhythmias,[48] cardiovascular instability during anesthesia,[17] and increased sensitivity to pressor amines. Serious ventricular arrhythmias have been observed in dogs treated with imipramine, anesthetized with halothane, and given pancuronium.‡ Similarly, arrhythmias are seen in cats treated with amitriptyline when anesthetized with halothane and given neostigmine for reversal of neuromuscular blockade.[17] Recommendations regarding the use of specific anesthetic agents in clinical practice cannot be made except to emphasize the importance of monitoring for arrhythmias.

Monamine Oxidase Inhibitors

Anesthesiologists should be wary of patients who are taking monamine oxidase inhibitors. Monamine oxidase (MAO) is an enzyme that catalyzes the breakdown of biogenic amines, such as dopamine and tyramine. The drugs are used as mood elevators to reverse depression. MAO-inhibiting drugs may have potentially dangerous interactions with a variety of drugs, including sympathomimetics, antidepressants, certain foods (such as cheese), and antihypertensive medications.[66]

Because MAO inhibitors enhance the effects of sympathetic amines and interfere with the detoxification of other drugs, patients who are taking MAO inhibitors may have cardiovascular instability and hypertensive crises during anesthesia as well as prolonged recovery from anesthesia.[20(pp180-184)] Common MAO inhibitors are listed in Table 1.

TABLE 1
Monamine Oxidase Inhibitors

Phenelzine (Nardil)
Nialamide (Niamid)
Isocarboxazid (Marplan)
Pargyline (Eutonyl)

Meperidine is specifically contraindicated in patients taking MAO inhibitors because its administration may result in excitation, sweating, rigidity, hypertension, hypotension, and even coma.[66] Other potent narcotics such as morphine appear less likely to cause untoward effects. Patients taking MAO inhibitors may have exaggerated responses to vasopressors and thus may not be good candidates for regional anesthesia.

A patient should not undergo elective surgery if he/she has taken MAO inhibitors within the past 2 weeks. If surgery is necessary, one should avoid narcotics, treat hypertension with direct-acting vasodilators (e.g., nitroprusside), and treat hypotension with fluids or carefully titrated quantities of direct-acting vasopressors.

Street Drugs

Patients using drugs obtained illicitly present particular problems regarding anesthetic management. Such "street" drugs include barbiturates, narcotics, cocaine, amphetamines, and phencyclidine derivatives (e.g., angel dust). Patients taking these drugs who must receive anesthesia may experience a wide variety of reactions, including hypertension, hypotension, altered anesthetic requirements, withdrawal crises, drug tolerance, and hepatitis. There are no general rules for care of these patients other than to obtain as good a drug history as possible and to titrate carefully any drugs administered during anesthesia. It is probably prudent to keep the anesthetic as simple as feasible to minimize the variables should an adverse reaction occur. In our opinion, inhalational anesthesia may be preferable.

Chemotherapeutic Drugs

Some of the drugs used for the treatment of cancer have important interactions with anesthetics. In a small study using rabbits, Bruce[6] found that the simultaneous administration of halothane and cyclophosphamide resulted in a 100% mortality. The mechanism for this interaction has not been found, and similar problems have not been reported in man.

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‡ Miller RD, personal communication.

Patients with cancer who are receiving chemotherapeutic drugs may also have an increased sensitivity to neuromuscular blocking drugs as a result of decreased plasma cholinesterase activity.§ The dosage of succinylcholine must thus be reduced.

Interaction of Inhalation Anesthetics

The cardiovascular effects of anesthetics may vary depending on other drugs that are administered coincidentally. As an example, the cardiovascular effects of nitrous oxide depend upon whether the drug is administered alone or in conjunction with diethyl ether, halothane, enflurane, or large doses of morphine (Table 2). In all circumstances, nitrous oxide causes an increase in total peripheral resistance. Cardiac output and blood pressure, however, are decreased when nitrous oxide is given alone[15] or in conjunction with morphine,[72] unchanged when given with halothane[70] or diethyl ether,[69] and increased when given with fluroxene.[68] Nitrous oxide has a negligible impact on the circulation during enflurane anesthesia.[67] The explanation for this variable effect of nitrous oxide when administered alone or in conjunction with other anesthetics is not known. One may speculate that nitrous oxide has a dual action: peripheral vasoconstriction, the magnitude of which is dependent upon preexisting vascular tone, and myocardial depression, which may be variably altered by the presence of other anesthetics.[15] The inhalation anesthetics may compete for similar receptor sites, and the affinity of each for those sites determines the overall effect of any combination. Alternatively, the variable cardiovascular effects of nitrous oxide may be due to a complex interaction at both central (sympathetic nervous system) and peripheral (myocardial, vascular) sites.

Despite the absence of data to explain the effects, it must be concluded that nitrous oxide is not an innocuous drug and that its action on the circulation may vary considerably when it is used in conjunction with other anesthetics.

Summary

Every anesthesiologist must have a thorough knowledge of pharmacology. A careful drug history should be taken on each patient and, if necessary, blood and urine samples should be analyzed for drug levels. If an unfamiliar drug is encountered when reviewing a patient's chart, a pharmacology textbook or the *Physician's Desk Reference* (PDR) should be consulted. The successful administration of an anesthetic involves careful selection of anesthetic agents, careful titration of anesthetic drugs, and a thorough knowledge of possible drug interactions.

TABLE 2

Cardiovascular Responses When Nitrous Oxide Is Added to Other Anesthetics (Percent Change from Control)

	Cardiac output	Heart rate	Peripheral resistance	Blood pressure
40% N_2O[15]	−19	−15	27	−3*
N_2O and halothane[70]	−3*	2*	15	11
N_2O and ether[69]	−5*	0*	19	12
N_2O and fluroxene[68]	11	7	11	22
N_2O and morphine[72]	−21	−8*	20	0*
N_2O and enflurane[67]	7*	−3*	0*	6*

* Not significant.

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Crystalloid versus Colloid

The effects of hemodynamic resuscitation with protein-containing or balanced salt solution were studied prospectively in 29 patients undergoing abdominal aortic surgery. Blood loss was replaced with packed red cells and extracellular volume with either Ringer's lactate (RL) or 5% albumin in Ringer's lactate (ALB). Fluids were given to maintain the pulmonary capillary wedge pressure (PCWP) equal to or within 5 torr above preoperative levels, the cardiac output (CO) equal to or greater than preoperative values, and the urine output at least 50 ml/hr. Serum colloid osmotic pressure (COP), CO, PCWP, the gradient between COP and PCWP (COP-PCWP), and intrapulmonary shunt (Qs/Qt) were measured preoperatively, intraoperatively, and daily for 3 days. The measured variables were similar preoperatively in both groups. Operation time, estimated blood loss, and transfusions were similar. Total fluids received on the day of operation were 11.3 ± 0.8 liters (RL) and 6.2 ± 0.4 liters (ALB). The maximum decrease in COP was 40% ($p < 0.001$) in the RL group while there was no significant change in the ALB group. The COP-PCWP decreased from 11 ± 1 to 2 ± 1 in the RL group ($p < 0.001$) and insignificantly in the ALB group. Qs/Qt increased slightly in both groups following operation but was not different between groups. Fluid balance, total fluid infused, sodium balance, total sodium infused, COP, or COP-PCWP did not significantly correlate with Qs/Qt. Two patients in the ALB group experienced pulmonary edema associated with normal COPs and elevated PCWPs. There were no cases of pulmonary edema associated with the low COPs and normal PCWPs in the crystalloid group. These data seriously question the necessity to maintain COP by using protein-containing solutions during acute hemodynamic resuscitation. When titrated to physiologic end points, even large volumes of balanced salt solutions are tolerated well. (*Virgilio RW, Rice CL, Smith DE, et al: Crystalloid vs colloid resuscitation: Is one better? A randomized clinical study. Surgery 85:129–139, 1979*)

CLINICAL reports

Progeria and Anesthesia

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James Kahre, MD†

Progeria or Hutchinson-Gilford syndrome is a rare disorder of children characterized by "premature aging." The following case report presents a patient with progeria who underwent general anesthesia on four occasions for correction of a dislocated hip.

Case Report

The patient was a 10-year old white girl referred for correction of a dislocated left hip. The procedure, originally scheduled at another hospital, was cancelled following unsuccessful attempts at tracheal intubation under general anesthesia.

She was born 2 weeks prematurely with a birth weight of 2.6 kg. The child was noted to be below normal for height and weight at 3 months of age. She was diagnosed as having progeria at 1 year of age after developing thinning of the skin and alopecia. The patient had normal mental development.

At age nine the patient suffered a cerebral vascular accident with left-sided hemiparesis. Although the paresis resolved within the next year, she developed a dislocation of the left hip some time after her stroke.

Physical examination at the time of admission revealed an emaciated, thin-skinned white girl with total alopecia. Height and weight were 110 cm and 11.2 kg, respectively. Both measurements were below the third percentile for this age. In addition to the dislocated left hip, physical examination revealed all the classic features of progeria: diminished subcutaneous fat, micrognathia, prominent scalp veins, abnormal dentition, pyriform thorax, thin limbs, prominent stiff joints, short stature, a thin, high-pitched voice, pointed beak-like nose, and the overall appearance of a plucked bird (figure).

Laboratory data were within normal limits. Chest x-ray revealed no evidence of cardiovascular or pulmonary disease. EKG was consistent with left ventricular hypertrophy.

Four procedures were performed for correction of the dislocated left hip. Initially an arthrogram with skeletal traction was performed. Open reduction of the dislocated hip was then accomplished followed by two cast changes. All procedures were accomplished under general anesthesia with induction either with N_2O and halothane or enflurane, or with thiopental. Maintenance of anesthesia was with halothane or enflurane in each instance. No muscle relaxants were used for any of the anesthetic techniques.

Deep general anesthesia was used for laryngoscopy at the time of the second operation. The glottic opening, visualized without difficulty; was, however, very narrow and appeared about 3.5 to 4.0 mm in diameter. Endotracheal intubation was not performed during any of the four general anesthetics to avoid possible postoperative airway obstruction from laryngeal edema. The lack of subcutaneous tissue led to some difficulty in maintaining an adequate mask fit.

The only significant postoperative problem was a persistent tachycardia following the open reduction. Volume replacement lowered the pulse rate transiently. The etiology of the tachycardia was not definitely determined. The patient is presently recovering at home.

Discussion

Progeria (premature aging, Hutchinson-Gilford syndrome) is a rare autosomal recessive disorder that usually becomes clinically apparent after 6 months of age. The incidence is about 1/8,000,000 live births in the United States. A total of 60 cases have been described in the world literature prior to 1972.[1]

The disorder, first described by Hutchinson in 1886,[2] was termed progeria by Gilford in 1901.[3] It occurs more frequently in the male population. The basic defect is unknown. Suggested possibilities include an immunologic basis or an enzyme deficiency involving DNA repair. There is no effective treatment presently available.

The progeria patient may develop all of the diseases of old age during the first or second decade of life.

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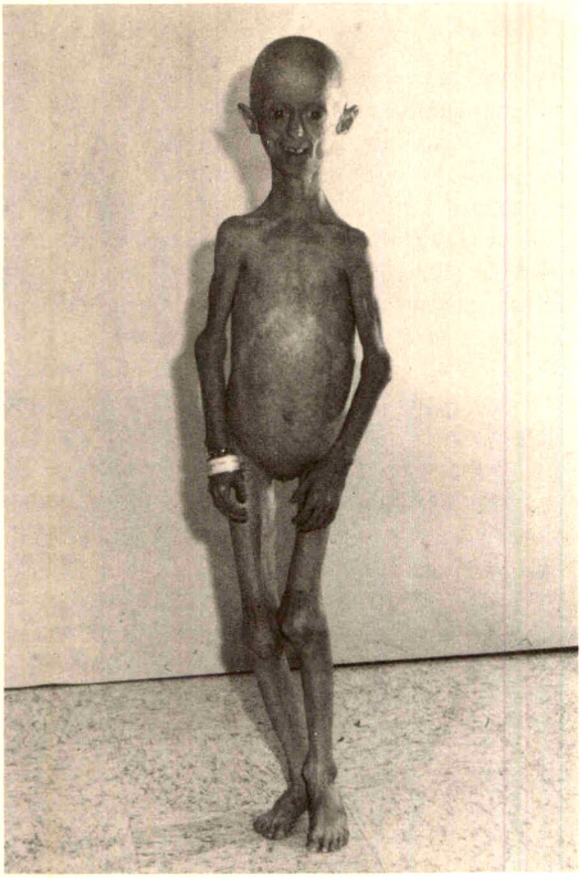

FIGURE. Patient at the time of admission to the hospital.

These may include ischemic heart disease with angina and myocardial infarction. Hypertension and cerebral vascular disease may also occur. Arthritis and diabetis mellitus have been reported.[1] Mean survival age is 13 years with death usually occurring by age 25 from congestive heart failure or myocardial infarction. Our patient had had a previous stroke and had left ventricular hypertrophy on EKG.

Several specific anesthetic considerations of the progeria patient should be emphasized. Mandibular hypoplasia and micrognathia may lead to difficulty in airway management and endotracheal intubation, although there was no difficulty in the case presented. The narrowed glottic opening, leading to the typical thin high-pitched voice, may require a smaller endotracheal tube than expected. The primary reason for referral to our institution was the failure of tracheal intubation. Even a minimal amount of swelling of the glottis may greatly compromise the airway and increase the resistance of airflow postoperatively. It may be best to avoid intubation if possible.

Preoperative evaluation of the cardiovascular system is necessary because of early incidence of atherosclerosis. Careful manipulation and positioning of the patient is necessary to avoid injury to thin, fragile limbs.

In summary, progeria is a rare disease characterized by early aging and early development of cardiovascular and cerebral vascular disease, together with micrognathia and a narrow glottis; the disease may present problems in anesthetic management.

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ANESTH ANALG
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Cimetidine for Prophylaxis of Aspiration Pneumonitis: Comparison of Intramuscular and Oral Dosage Schedules

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Aspiration of gastric contents into the tracheobronchial tree is a major cause of anesthesia-related morbidity and mortality.[1] Silent regurgitation of gastric contents occurs more frequently than is realized, even with an endotracheal tube in place.[2, 3] A pH value of less than 2.5 is generally considered the critical level for the development of pulmonary damage.[4, 5] Routine antacid prophylaxis is established practice in obstetric anesthesia and has been advocated for all anesthesia.[6, 7] Cimetidine, a new histamine-2 receptor antagonist,[8] increases gastric pH and decreases gastric volume.[9] A number of studies have recently evaluated the efficacy of oral doses of cimetidine premedication at raising gastric pH.[10-12] The aim of this study was to compare intramuscular with oral doses of cimetidine along with routine premedication for elective surgery with respect to increasing gastric pH.

Methods

Twenty-six consenting adult patients, A.S.A. class I or II, scheduled for 8 a.m. elective surgery requiring an endotracheal intubation, were studied. All patients fasted after midnight and were premedicated with morphine sulfate, 0.1 to 0.2 mg/kg at 6:30 a.m. Patients were randomly assigned to three groups. Groups were similar with regard to weight, age, and sex. Group 1 received no additional premedication. Group 2 received cimetidine, 300 mg orally (p.o.), at bedtime and 300 mg p.o. at 6:30 a.m. with less than 30 ml of water. Group 3 received cimetidine, 300 mg p.o., at bedtime and 300 mg IM at 6:30 a.m.

To evaluate the necessity for a bedtime dose, 10 additional patients (group 4) received oral cimetidine, 300 mg, 90 minutes prior to surgery without a preceding dose. Anesthesia was induced with thiopental, and tracheal intubation was accomplished with the aid of succinylcholine. A no. 16 nasogastric tube was passed immediately following intubation and all available gastric contents evacuated. The volume and pH of the gastric contents were measured.

All pH values were measured with a Beckman 76008 digital pH meter and no. 39183 probe combination electrode. The gastric volumes obtained are not considered to represent accurately the total volume of the gastric contents as no attempt was made to fully empty the stomach by altering the position of the patients. The three groups were compared with respect to pH values by a one-way analysis of variance and a multiple comparison test.[13] Group 4 was compared to group 1 with respect to pH values by an unpaired t-test.[14] The level of statistical significance used was less than or equal to 0.05.

Results

The mean pH values of the gastric aspirates are shown in the Table. The distribution of pH values are shown in the Figure. The groups that received cimetidine, 300 mg p.o. at bedtime and 300 mg either p.o. or IM at 6:30 a.m., had gastric aspirates with pH levels significantly higher than the control group when measured 90 minutes later. The group receiving cimetidine intramuscularly had gastric aspirates with significantly higher pH levels than the group receiving the drug orally. One patient who received cimetidine orally had a pH below 2.5.

Patients receiving only cimetidine, 300 mg p.o. at 6:30 a.m., had gastric aspirates that were not significantly different from the pH levels of control patients. Three patients in this latter group had pH values less than 2.5.

Gastric juice could not be obtained from six patients who were not included in the study.

Discussion

The peak effect of cimetidine on gastric pH occurs 4 to 6 hours after oral administration.[12] Stoelting[10] found that 300 mg of cimetidine given orally 90 minutes before induction of anesthesia increased gastric pH to levels above 2.5 in some but not all patients.

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TABLE
Gastric Residue from Cimetidine-Treated and Control Patients

	Control patients	Cimetidine-treated patients		
		300 mg p.o. h.s. 300 mg p.o. a.m.	300 mg p.o. h.s. 300 mg i.m. a.m.	300 mg p.o. a.m.
Total patients	10	10	6	10
pH (mean ± SEM)	2.92 ± 0.49	5.1 ± 0.61	7.3 ± 0.31	4.4 ± 0.74
Range	1.7–6.34	2.2–7.5	6.4–8.1	1.4–7.4
p value		<0.05*	<0.05*	NS†

* Group 2 and Group 3 were significantly different from each other as well as from the control group.
† NS, not significant.

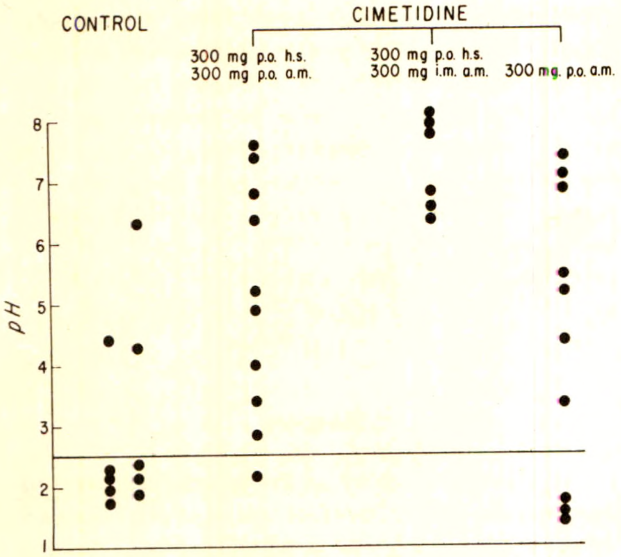

FIGURE. Distribution of gastric aspirate pH values in control and cimetidine-treated patients.

Keating et al[11] supplemented pre-anesthetic medication with a bedtime oral dose of cimetidine but seven of 31 patients had gastric pH values of less than 2.5.

Walkenstein et al[15] in comparing the availability of oral and parenteral cimetidine found that a 300-mg intramuscular dose produced blood levels at 90 minutes that were almost twice those achieved by an equivalent oral dose.

To increase the number of patients with an adequate response to cimetidine, that is, a gastric pH above 2.5, we administered the drug by mouth at bedtime and as an intramuscular injection 90 minutes prior to induction of anesthesia. This was more effective in raising gastric pH levels than oral cimetidine, although the number of patients is small. Our results suggest that premedication with intramuscular cimetidine produces a greater and more consistent rise in gastric pH than does oral cimetidine.

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Right Radial Artery Pressure during Mediastinoscopy

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Mediastinoscopy has been recommended in all patients prior to thoracotomy for pulmonary carcinoma.[1] The technique for mediastinoscopy originally described by Carlens[2] and with various modifications[3, 4] has proven to have a morbidity of less than 3%.[1, 5]

Compression of the innominate artery during mediastinoscopy with loss of the right radial pulse has led to the erroneous diagnosis of cardiac arrest.[6] One case of transient left hemiparesis has been reported and was attributed to compression of the innominate artery by the mediastinoscope.[5] Early investigators[5] recommended monitoring of the right radial pulse because of innominate artery compression during "vigorous retraction on the mediastinoscope." Recently, Lee and Salvatore[6] have advocated constant monitoring of the right radial pulse by plethysmography and judicious monitoring of the carotid artery blood flow by Doppler probe in patients with significant arteriosclerotic disease.

Frequency and duration of alterations in right radial artery pressure during mediastinoscopy have not been documented and are the purpose of this study.

Methods and Materials

Seven patients scheduled for bronchoscopy and mediastinoscopy were studied. A 20-gauge Teflon catheter was placed in the right radial artery and the pressure tracing recorded on a continuous readout strip chart. A blood pressure cuff was placed on the left arm. Each patient was monitored with a three lead EKG and esophageal stethescope. General anesthesia was induced with thiopental and maintained with halothane, nitrous oxide, and oxygen. Following completion of bronchoscopy, mediastinoscopy was performed through a small suprasternal incision. After incising the platysma and the pretracheal fascia, the trachea was exposed below the isthmus of the thyroid gland. A tunnel was then developed by blunt dissection behind the aortic arch into the right paratracheal region.[7] The mediastinoscope or bivalve speculum is then introduced into the tunnel (Figure) and biopsies are taken of suspicious lymph nodes. A bivalve speculum was used in three patients and a mediastinoscope[4] in four patients. The chart recorder was turned on prior to insertion of the mediastinoscope or bivalve speculum and run continuously during mediastinoscopy. The chart recordings were analyzed for duration and magnitude of decrease in the right radial artery pressure.

Results

Four of the seven patients (see Table) had a decrease in right radial artery pressure during mediastinoscopy. There were 48 episodes of right radial artery hypotension lasting from 15 to 360 seconds. The lowest pressure was 25/0 mm Hg and lasted 30 seconds. The longest duration of a decrease in pressure was 360 seconds at a pressure of 50/43 mm Hg. In one patient, with a radial pressure of 160/80 mm Hg prior to mediastinoscopy, the pressure decreased to 40/30 mm Hg on five occasions lasting 15 to 120 seconds.

No changes in left arm blood pressures were noted during alterations in the right artery pressure. Heart rate, EKG, and esophageal heart tones remained unchanged during mediastinoscopy. Frequency and magnitude of radial arterial hypotension were the same with the bivalve speculum and with the mediastinoscope.

Discussion

The extent of injury resulting from a decrease in right radial artery pressure from 80/60 mm Hg to 50/40 mm Hg for a period of 360 seconds in the supine position cannot be estimated. The report of one patient with transient left hemiparesis early in the development of mediastinoscopy[5] is difficult to evaluate.

Disappearance of the right radial artery pulse is most likely due to compression of the innominate artery by the mediastinoscope. The Figure shows the anatomical relationship of the mediastinoscope to the tracheal lymph nodes and to branches of the aortic arch. Compression during introduction of the mediastinoscope or manipulation to expose peritracheal nodes could compress the innominate artery with loss

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TABLE

Right Radial Artery Pressure during Mediastinoscopy

Patient	Type of equipment	Pressure			Duration of each alteration in pressure in right arm
		Prior to mediastinoscopy	During mediastinoscopy		
			Left arm	Right arm	
			mmHg		*sec*
F.E.*	Bivalve speculum	160/80	160/80	75/50	15, 15, 15, 20, 15, 15, 15
			160/80	40/30	15, 15, 60, 45, 120
C.M.	Bivalve speculum	140/70	No change		
E.B.	Bivalve speculum	80/60	80/60	50/40	75, 60, 90, 60, 360
				25/0	
A.P.	Mediastinoscope	110/60	No change		
D.S.	Mediastinoscope	110/60	110/60	95/50	180
			110/60	75/60	115
			110/60	70/50	30, 60, 15, 15, 30, 180
			110/60	50/40	115, 45, 15, 15
J.K.	Mediastinoscope	110/75	No change		
L.I.	Mediastinoscope	130/90	130/90	90/50	60, 30, 30, 15, 15, 150, 45

* The recorded pressure in the right radial artery was 75/50 and occurred seven times during use of the bivalve speculum in episodes lasting 15 to 20 seconds.

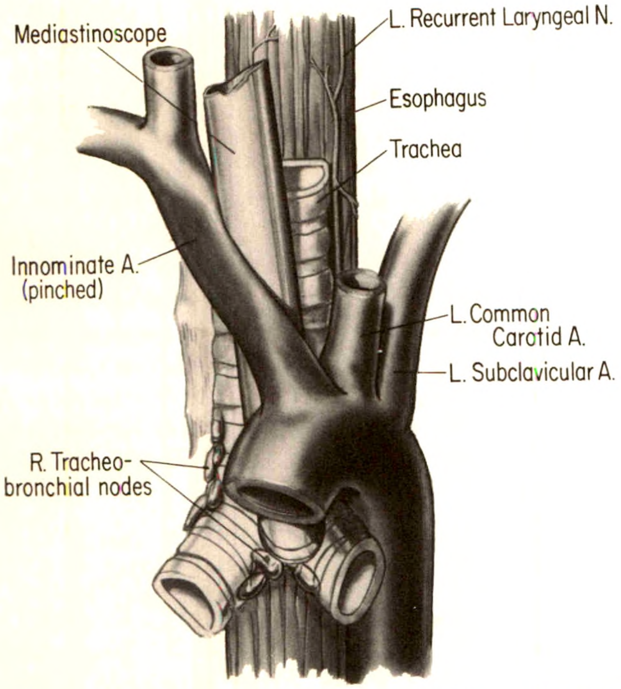

FIGURE. Mediastinoscope within the mediastinum. Note the pinched innominate artery.

of blood flow in the right subclavian and carotid arteries.

The disappearance of the right radial pulse during mediastinoscopy must be correlated with the left radial artery pulse or carotid pulse. The false diagnosis of cardiac arrest during anesthesia is both distressing and time consuming and leads to unnecessary interruption of the surgical procedure.

The complication rate is low during mediastinoscopy but when complications do occur they may be catastrophic. Massive hemorrhage, air embolism, tracheal laceration, pneumothorax, and other complications necessitate careful monitoring during mediastinoscopy. The author recommends the use of a blood pressure cuff on the left arm and finger plethysmograph or monitoring of the right radial artery by palpation during mediastinoscopy. Any change in the right radial pulse is an indication for repositioning of the mediastinoscope. Caution should be taken in those patients with possible impaired cerebral circulation, i.e., bilateral carotid artery stenosis, history of strokes, etc. Evaluation of changes in cerebral blood flow during compression of the innominate artery can, however, only be accomplished with sophisticated measurements of cerebral blood flow since Doppler monitoring of a single carotid artery does not reflect cerebral blood flow.

In summary, right radial artery pressure was monitored continuously during mediastinoscopy in seven patients. Major alterations in pressure lasting 15 to 360 seconds occurred due to compression of the innominate artery in four patients. It is recommended that during mediastinoscopy patients have a blood pressure cuff on the left arm and that the right radial artery pulse be constantly palpated.

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Complications from Use of Carlens Tubes

Five cases of tracheobronchial rupture are reported in a series of 2,700 patients intubated with Carlens tracheal tubes for a variety of intrathoracic procedures. Tracheobronchial rupture was diagnosed intraoperatively in three patients, and in the early postoperative period in the remaining two patients. All patients required direct repair of the tracheobronchial injuries. The authors suggest that factors leading to the complications include use of inappropriate sizes of tracheal tubes, tube malpositioning, and rapid inflation of the tube cuffs. The possibility of airway injury produced by double-lumen tubes should be considered in the differential diagnosis of perioperative respiratory problems in appropriate patients. (*Guernelli N, Bragagiia RB, Briccoli A, et al: Tracheobronchial ruptures due to cuffed Carlens tubes. Ann Thorac Surg 28:66–68, 1979*)

Nitroprusside Use in Mitral and Aortic Regurgitation

To compare the hemodynamic effects of vasodilator therapy on different regurgitant lesions, sodium nitroprusside was administered intraoperatively in 12 patients with mitral regurgitation and in 15 with aortic regurgitation. During the period preceding establishment of cardiopulmonary bypass, both groups had developed intense vasoconstriction and cardiac decompensation. All demonstrated improved cardiac function with vasodilator therapy; however, the degree of improvement with nitroprusside differed in the two groups. Stroke volume increased 10 ml/beat/m^2 in those patients with aortic regurgitation and only 6 ml/beat/m^2 in those with mitral regurgitation ($p < 0.05$). The percent increase in stroke volume induced by nitroprusside was inversely correlated to the preoperative left ventricular ejection fraction ($r = -0.44$, $p < 0.02$). Patients with aortic regurgitation had lower preoperative left ventricular ejection fractions than those with mitral regurgitation (0.53 vs 0.63, $p < 0.02$). The authors conclude that patients with aortic regurgitation derived greater intraoperative hemodynamic benefit from "unloading" with nitroprusside, because they came to surgery with greater impairment of left ventricular contractility. Although nitroprusside improved cardiac function in both groups, only the patients with aortic regurgitation achieved normal pulmonary artery pressure (17 torr) and pulmonary vascular resistance (2.1 units) as a result of "unloading." Those with mitral regurgitation continued to have pulmonary hypertension (28 torr) and increased pulmonary vascular resistance (3.9 units) despite vasodilator therapy. Thus the data suggest that patients with mitral regurgitation derived less hemodynamic benefit from intraoperative nitroprusside therapy because they were also limited by right ventricular dysfunction and a less responsive pulmonary vasculature. (*Stone JG, Hoar PF, Faltas AN, et al: Comparison of intraoperative nitroprusside unloading in mitral and aortic regurgitation. J Thorac Cardiovasc Surg 78:103–109, 1979*)

ANESTH ANALG
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Anesthesia for Extensive Resection of Congenital Tracheal Stenosis in an Infant

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Congenital tracheal stenosis is an extremely rare anomaly. Untreated, the lesion has been almost uniformly lethal. Certain types of this anomaly, however, are amenable to surgical correction.[1,2] The lesion is frequently associated with other anomalies particularly of the bronchi, lungs, and great vessels, as well as other organs. Cantrell[1] classified congenital tracheal stenosis in three morphologic types: generalized hypoplasia, funnel-like stenosis, and segmental or hourglass stenosis.

This paper reports the successful resection of a congenital hourglass-type tracheal stenosis in a 4-month-old male infant. Anesthetic and postoperative management are described.

Case Report

A 4-month-old, 6.5-kg white male infant was admitted in acute respiratory distress with loud inspiratory stridor and chest wall retraction. The respiratory rate was 80/min, pulse rate 180/min, systolic blood pressure 96 torr by palpation, and temperature 37.8 C. Breath sounds were obscured by the stridor. The left tympanic membrane was dull and bulging with the evidence of pus behind it. The remaining physical examination was normal. The parents stated that the patient's breathing had often been accompanied by a "snoozing" sound since birth. Hemoglobin was 11.6 g%, white blood count 19,700, and urinalysis 2+ for acetone. Arterial blood gas values while breathing room air were pH 7.31, Pa_{O_2} 52 torr, and Pa_{CO_2} 45 torr. The chest roentgenogram and electrocardiogram were normal. The patient was treated with ampicillin for otitis media and with oxygen and racemic epinephrine for upper airway obstruction. The respiratory distress improved.

A barium swallow showed no abnormality of the esophagus or great vessels. Tomograms of the larynx and trachea, however, were consistent with an hourglass stenosis involving the mid-portion of the trachea for approximately 15 mm, which was almost 50% of the length of the infant's trachea, with suggestion of complete rings (Fig 1). Diagnostic bronchoscopy was performed on the 5th day. The infant was not in respiratory distress at this time when breathing room air. The pulse rate was 140/min, respiratory rate 40/min, and temperature 37.6 C. The infant was premedicated with atropine, 0.1 mg IM. Anesthesia was induced with halothane in a 50% mixture of N_2O and O_2, using a high-flow non-rebreathing system and then maintained with 1.5% halothane in oxygen. Blood pressure was monitored with a Doppler apparatus; the electrocardiogram and temperature were monitored continuously. With the aid of succinylcholine, 10 mg IV, the vocal cords were visualized with a 3-mm Stortz pediatric bronchoscope, but the bronchoscope could not be advanced through the stenotic area of trachea. The patient was ventilated by mask with 1.5% halothane in oxygen again. The 2.5-mm bronchoscope also could not be advanced. A small inner telescope, 1.5 mm in diameter, passed through the area of stenosis. Laryngospasm occurred upon removal of inner telescope; treatment was atropine, 0.1 mg, and succinylcholine, 10 mg IV. Postoperatively the infant developed respiratory distress with stridor and chest wall retraction, which were treated with dexamethasone, 1 mg IV every 6 hours, and racemic epinephrine every 3 hours. The bronchoscopy confirmed the absence of a membranaceous trachea and the presence of complete rings in the area of stenosis, and confirmed that the larynx, carina, and mainstem bronchi were normal.

Respiratory distress continued and surgical correction was undertaken 2 weeks later. The preoperative pulse rate was 150/min, respiratory rate 40/min, and temperature 37.2 C. Mild inspiratory stridor and chest wall retraction were present only during crying. Hemoglobin was 12.0 g%, white blood count 12,400; electrolytes were within normal limits. The infant was premedicated with atropine, 0.1 mg, and hydrocortisone, 20 mg IM. Anesthesia was induced with ketamine, 25 mg IM, and maintained with 1.5% to 0.75% halothane in oxygen using a high-flow non-rebreathing system. With the knowledge that the tracheal stenosis began almost 1 cm distal to the cords, a 3-mm Portex endotracheal tube was advanced as far distally as possible and secured well. The tracheal intubation was facilitated with succinylcholine, 10 mg IV. Respiration was controlled during the operation. The infant's circulation was monitored with an esophageal stethoscope, continuous oscillographic display of ECG, and arterial pressure. Temperature was monitored with a rectal thermistor probe.

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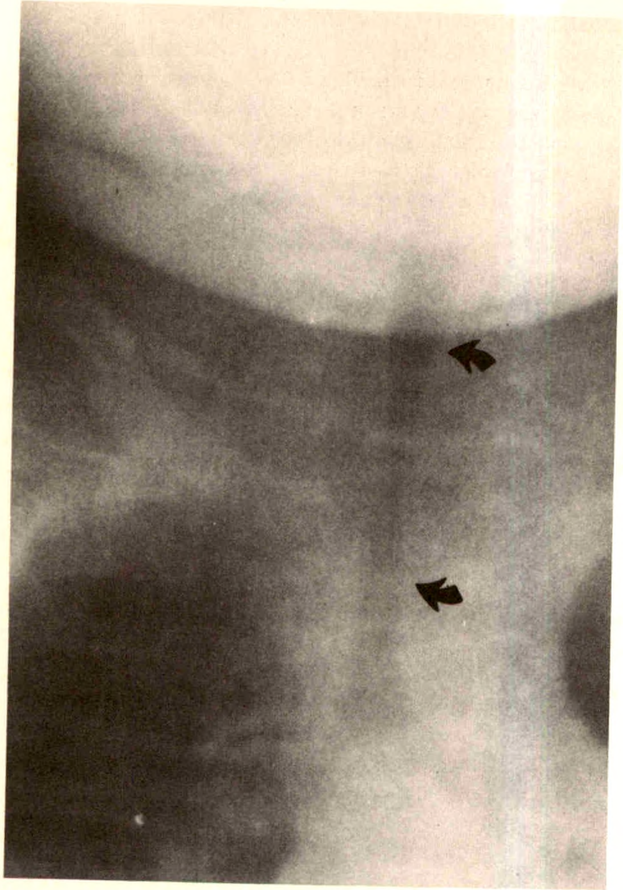

FIG 1. Tomogram on admission showing extensive tracheal stenosis.

With the cardiopulmonary bypass pump team standing by, a transverse incision was made in the neck. The entire trachea was freed through the same incision. The dissection was also carried down to the carina to obtain its maximal mobilization. The stenosis began at the sixth tracheal ring and continued distally for nine rings. A vertical incision was made in the lower portion of the stenotic area through the 14th tracheal ring. A sterile 4-mm Portex tube was passed distally through this incision into the nonstenotic trachea and secured in place with umbilical tape. The patient was ventilated through this endotracheal tube. The stenotic portion of the trachea, measuring 17 mm in length including nine tracheal rings, was then resected. After circumferential interrupted sutures were in place between the two ends, another sterile 4-mm Portex endotracheal tube coated with cortisone cream was passed retrogradely through the open transected proximal trachea, the larynx, into the mouth, and out (Fig 2). This endotracheal tube was connected to the anesthetic system and the distal end was inserted into the distal trachea after removing the other tube. The infant's head was then repositioned in maximal flexion, and primary repair of the trachea was completed. At the end of the surgery, the infant's chin was stitched to the anterior chest wall with five 0-Prolene sutures. A posterior splint was then also applied from the head to the buttocks to prevent extension of the neck. Operating time was 4 hours 30 minutes. In order to ensure immobilization and to allow the infant to become accustomed to the extreme flexion of the neck in the immediate postoperative period, pancuronium used during surgery (1.2 mg) was not reversed but instead the infant was ventilated using a Bournes respirator. With a F_{IO_2} of 0.6, arterial blood gas values were pH 7.50, P_{aCO_2} 24 torr, and P_{aO_2} 158 torr. Antibiotics included cephalothin and gentamycin; dexamethasone, 0.5 mg IV every 6 hours, was resumed. The infant was weaned from the respirator using intermittent mandatory ventilation 20/min which was gradually reduced to 5/min over a period of 6 hours 45 minutes. The patient then breathed spontaneously through a T-piece for 1 hour 30 minutes, during which time with a F_{IO_2} of 0.4, arterial blood gas values were pH 7.39, P_{aCO_2} 28 torr, and P_{aO_2} 187 torr. The infant was fully awake. With a tracheotomy tray open at the bedside, the endotracheal tube was removed without incident 8 hours 15 minutes postoperatively. The respiratory rate following extubation was 40/min, the pulse rate 150/min, and the temperature 37.8 C. The subsequent hospital course was uneventful. Dexamethasone was gradually decreased to 0.125 mg by mouth every 12 hours and stopped on the 8th postoperative day. The posterior splint was removed on the 2nd postoperative day. The chin stitches were removed 3 weeks later. The infant was discharged from the hospital 4 weeks after surgery. A tomogram of the trachea taken 4 weeks after surgery was within normal limits.

Discussion

Thirty-five cases of congenital tracheal stenosis without pulmonary-artery sling have been reported in the literature.[1-5] All were in infants and children with the exception of one case reported by Stewart and Pinkerton.[4] One case was stillborn and the majority of the patients died of acute respiratory distress. Five patients improved following tracheal dilation but

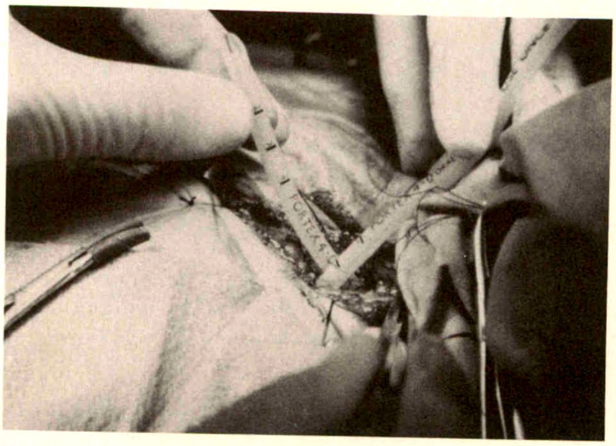

FIG 2. Retrograde tracheal intubation with a sterile endotracheal tube.

the follow-up of these patients is not documented.[2] Recently two patients, a 7-year-old girl[1] and a patient whose age was not specified,[2] underwent successful surgical correction by resection of the lesion and end-to-end anastomosis of the trachea.

Advances made in pediatric airway management and respiratory care have increased the incidence of acquired tracheal stenosis in infants and children. Acquired tracheal stenosis following prolonged endotracheal intubation is most often subglottic at the level of cricoid cartilage[6] whereas stenosis following tracheostomy is usually at the site of stoma or near where the tip of the cannula lay.[7-9] Treatment for acquired stenosis includes repeated dilation, insertion of a stent, and resection with end-to-end anastomosis when the stenosis lies in the middle or lower part of the trachea. Acquired stenosis is, however, usually not as extensive as congenital stenosis.[10, 11]

Experimental studies in cadavers indicate that with proper mobilization of hilar area and maximal cervical flexion nearly 50% or more of the trachea can be resected in the adult.[12] Preoperative evaluation of our infant indicated that up to 50% resection of the trachea would be possible with extreme cervical flexion. Because of the cervical flexion we anticipated postoperative difficulty at the time of extubation. Our objectives in the anesthetic and postoperative management, therefore, were to secure the airway and have the infant gradually become accustomed to the endotracheal tube and to maximal cervical flexion before extubation.

The induction of anesthesia with a small dose of ketamine avoided excitement and the transition to halothane anesthesia was smoothly accomplished in our infant. A 3-mm Portex tube advanced as far as possible into the stenotic area could be well secured. Ventilation was easily maintained through this tube as well as through the sterile 4-mm Portex tube later inserted below the stenotic area. Tracheal intubation under heavy drapes in a small infant may be difficult, particularly when the operative area is in the neck, and so retrograde tracheal intubation with a sterile 4-mm Portex tube was performed by the surgeon at the final stage of reconstruction. This technique may also be of potential value in reducing wound infection.[13] Postoperatively the infant was mechanically ventilated and remained immobilized in maximal cervical flexion with a posterior splint and with the chin stitched to the chest. Chest and neck roentgenograms ruled out air leaks from the site of anastomosis during this period of time. When disconnected from the respirator, the infant was fully awake and the endotracheal tube was well tolerated. Despite our concern about potential upper airway obstruction, the extubation was uneventful.

In cases such as this, efforts should be made to avoid postoperative laryngeal edema by immobilization of the head and endotracheal tube, by use of a proper size endotracheal tube, and by administration of steroids systemically. The infant should be fully awake and acclimated to his environment before extubation. Although the above recommendations are not substantially different from routine airway care in infants, we believe these are particularly important in cases in which maximal cervical flexion and immobilization are required postoperatively.

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Cervical Spondylosis and Difficult Intubation

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An unusual cause of difficult endotracheal intubation in a patient with cervical osteoarthritis is described.

Case Report

The patient was a 73-year-old man with a long history of osteoarthritis, Paget's disease, arteriosclerotic peripheral vascular disease, and adult-onset diet-controlled diabetes mellitus. He was functioning well in his daily life without any medication. There was no history of cardiopulmonary disease.

Past history included a radical prostatectomy in June 1977, followed by repeated urethroscopy and urethral dilation procedures. General anesthetics for these were administered using a facemask and an oropharyngeal airway without difficulty. On no occasion did preoperative questioning or examination disclose symptoms or signs of airway difficulty or limitation of neck motion. In May 1978 during urethroscopy and urethral dilation under general anesthesia, the patient developed upper airway obstruction immediately after induction of general anesthesia with 250 mg of thiopental. It was very difficult to ventilate him with an oropharyngeal airway and facemask. An attempted orotracheal intubation and, finally, the anesthetic itself were abandoned because of the airway problem. During this laryngoscopy we noted that the trachea was deviated to the right, and the epiglottis to the left. A full set of capped upper teeth also complicated the intubation efforts.

Because of the suspicion of new growth behind the larynx causing the abnormal anatomy we saw, direct laryngoscopic examination using bilateral superior laryngeal nerve blocks and topical anesthesia was performed by an otolaryngologist. This showed a mass posterior to the larynx which impinged on the thyroid cartilage and pushed the glottis to the left. The laryngeal lumen was patent and the cords were normal in appearance and movement. In order to further characterize the laryngeal distortion, tomograms of the larynx and an esophagogram were done.

The tomograms of the larynx (Fig 1) showed deformity of thyroid and cricoid cartilage with some tilting, high on the right and low on the left. There was a redundant soft tissue density in the glottic and supraglottic areas, slightly more on the left than on the right side due to extrinsic pressure from hypertrophic bony changes on the anterior aspects of the C-5, C-6, and C-7 vetebral bodies. An esophogram (Fig 2) confirmed the presence of these degenerative osteoarthritic changes in the cervical spine with exuberant osteophyte formation anteriorly. The osteophytes also caused deformity on the posterior aspect of the cervical esophagus.

Despite thorough discussion of his airway and the implications and possible dangers of general anesthesia, the patient remained strongly opposed to any form of regional anesthesia. Two general anesthetics were subsequently administered for urethroscopy, and for urethroplasty and pubectomy after we had identified the causes of difficulty in maintenance of a clear airway. Awake orotracheal intubations were twice successfully accomplished with a no. 3 Miller blade and a 7-mm i.d. Portex endotracheal tube passed through the left mouth angle after bilateral superior laryngeal nerve blocks with 2% lidocaine and a benzocaine-tetracaine mixture (Cetacaine) for topical anesthesia. The general anesthetics otherwise proceeded uneventfully after these intubations.

Discussion

There are treatable or reversible causes for airway obstruction that are similar to this case; these causes include epiglottitis, abscess, or other soft tissue swelling. This patient's condition represents a nonreversible, extremely unusual cause of difficult endotracheal intubation. That repeated uneventful general anesthetics were given prior to the airway obstruction that occurred after thiopental induction in May 1978 suggests that the patient's anatomical distortion was a progressive osteoarthritic process.

Osteoarthritis is a noninflammatory disorder of movable joints characterized by progressive deterioration and abrasions of articular cartilage, and also by formation of new bone at the joint surfaces.[1] Cervical spondylosis is a condition in which there is progressive degeneration of the intervertebral discs leading to changes in the surrounding structures, especially the bone and meninges. In the past this condition has been called osteoarthritis, cervical spondylitis, herniated disc, chondroma, etc, but the term spondylosis is considered preferable as the condition is a degenerative rather than inflammatory or neoplastic one. In

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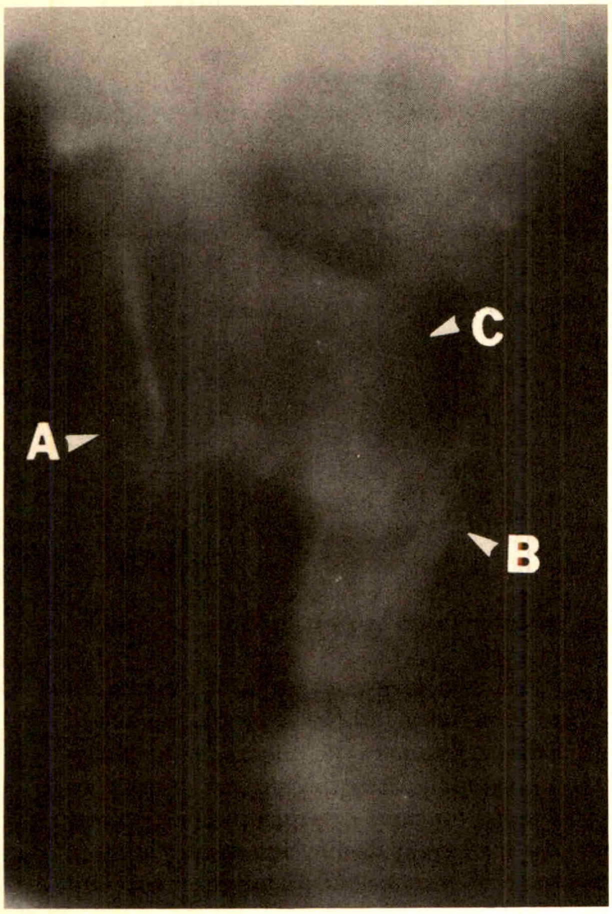

FIG 1. Anterior-posterior view of a tomogram of larynx showing marked distortion of the thyroid cartilages displacing the right side of the larynx upward (A) and the left side downward (B) and a large soft tissue density in the glottic and supraglottic areas (C).

cervical spondylosis osteophytes may occur at any point on the margins of the vertebral bodies. The formation of osteophytes is probably secondary to degenerative and/or traumatic lesions of the intervertebral discs and of the articular cartilages of the vertebral bodies. The osteophytes project outward from the margin of the vertebral bodies, and cracks and erosions may be present in the articular cartilages.[2] Interestingly, the osteophytes of the anterior aspect of cervical spine in this patient were not large enough to cause difficult intubation in June 1977 when he had a radical prostatectomy and the osteophytes did not cause any airway obstruction during several other general anesthetics until May 1978.

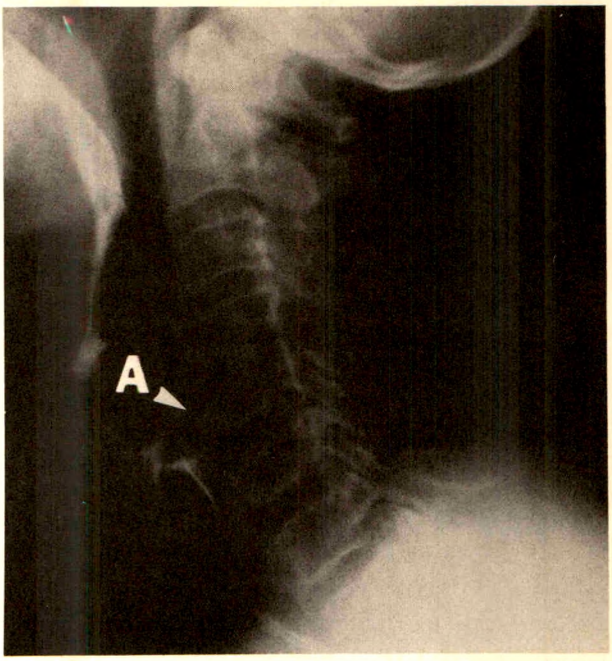

FIG 2. Lateral view of cervical area during esophogram. There is exuberant osteophyte formation anteriorly (A), which causes pressure on the posterior aspect of the cervical esophagus.

The diagnosis of Paget's disease of the left iliac wing of the pelvis was suggested from the radiologic appearance during intravenous pyelography and an elevated serum alkaline phosphatase. However, there were neither radiologic evidence nor clinical signs and symptoms of Paget's disease of the cervical spine in our patient.

A review of the literature disclosed no other reports of airway compromise by cervical spondylosis. We conclude that cervical osteophytic changes should be considered as possible cause for airway impairment in elderly patients with osteoarthritis and that anesthesiologists should be prepared to adjust their airway management techniques when necessary.

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Phantom Tongue Pain and Causalgia: Case Presentation and Treatment

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An unreported phenomenon of painful phantom tongue was observed following glossectomy and radical cancer surgery. It was associated with altered sympathetic activity or causalgia of the cheeks and temporal regions. Pain relief was effected by repetitive stellate ganglion blocks.

Case Report

A 59-year-old man with carcinoma of the tongue was evaluated in March 1978 for surgical resection after radiotherapy. The tumor grossly involved the anterior two thirds of the tongue and was associated with tongue pain described as a continuous dull ache with a sharp, stabbing quality on mastication. The patient underwent total glossectomy, total laryngectomy, left radical neck dissection, and creation of a permanent tracheostomy and deltopectoral flap. Following surgery he continued to perceive the cancerous tongue that moved with swallowing and attempted phonation. Burning pain was also present in the illusionary tongue. Within a few days he experienced constant bilateral aching and burning pain in the cheeks and temporal regions, greater on the left side than on the right. There was also intermittent stabbing pain in the left mandibular area. Minimal relief was afforded by a preparation consisting of phenacetin and caffeine with 30 mg of codeine (Empirin #3) combined with a preparation consisting of aspirin, phenacetin, and caffeine with 4.5 mg of oxycodone hydrochloride and 0.38 mg of oxycodone terephthalate (Percodan). The patient persisted in abusing these drugs. Because of inability to eat or sleep, intolerance to hot and cold stimuli, as well as facial pain he was referred to our pain clinic in October 1978.

Physical examination revealed marked induration and hyperemia of the left face and submaxillary area with a surgical scar extending over the left neck, shoulder, and chest. There was hyperesthesia of the skin of the left lower face not associated with paresthesias or numbness. There was generalized tenderness over the left anterior chest and a trigger point could be demonstrated medially on the remaining left mandible, pressure on which precipitated stabbing left facial pain.

The patient underwent a diagnostic left stellate ganglion block with 6 ml of 0.25% bupivacaine. He reported 60% improvement of the burning facial pain and relief of the painful phantom tongue. Over the next 2 days the facial and phantom pain gradually returned, but to a lesser degree allowing the patient to voluntarily reduce his use of analgesics. Because of the successful diagnostic block, a series of five stellate ganglion blocks was performed. The patient also received 50 mg of amitriptyline at night. The blocks were performed on alternate days using 8 ml of 0.25% bupivacaine with 1/200,000 epinephrine. Following each block he experienced increasing duration and degree of relief of his burning, aching, lingual and facial pain. After the third block there was complete pain relief that persisted through the series of blocks and continued beyond 3 months. Intermittently he has continued to have the sensation of a phantom tongue, though now painless.

Discussion

Development of phantom phenomena occurs in 90 to 100% of extremity amputees.[1] The ghost limb is painless and normally shaped and with time may fade or telescope. Phantom sensations have also been reported after loss of a nose, breast, or penis.[2] It has been estimated that 2 to 10% of patients with phantom limb sensation develop pathologic limb pain.[3]

Our case of painful phantom tongue meets the criteria for phantom limb pain described by Melzack:[4] (1) pain continues beyond healing; (2) trigger zones may spread to healthy areas; (3) phantom pain develops in patients who have suffered pain prior to amputation; and, (4) pain is abolished by increases or by decreases in somatic sensory input. The phantom tongue pain in our patient was described as burning. Painful phantom limbs have also been described as burning.[2, 5–7] In addition, our patient developed causalgia of the cheeks and temporal regions manifested by edema, hyperesthesia, and burning pain. Causalgia is known to develop after nerve injury and may have resulted from surgical nerve damage in this patient. Sympathetic nervous system abnormalities have likewise been observed in patients with painful phantom limbs. Vasomotor changes may be evident in the stump and remaining extremity manifested by sweating and hypersensitivity.[2, 8] The role of the sympathetic activity associated with micturation, defecation,

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and ejaculation have been reported to aggravate phantom limb pain.[6]

The etiology of phantom limb pain is unknown. The narcissistic theory of self-denial of a missing body part[9] suggests a possible psychological origin as does a grief reaction.[10] The occurrence of phantom limb pain is related to age, culture, social class, education, and occupation; it develops most frequently in elderly, skilled workers without higher education.[5] Phantom limb pain has also been attributed to irritation of the peripheral nerves or neuroma formation. A central mechanism has been suggested consisting of an abnormal reverberating pattern of firing in the internuncial pool in the dorsal horn of the spinal cord.[11, 12] The reticular formation has also been suggested as acting as a central biasing mechanism[4] exerting a tonic inhibitory role on transmission through all synaptic levels. Amputation of a limb decreases the sensory input into the reticular formation and thus allows self-sustaining neural activity at all levels.

The painful phantom tongue experienced by our patient is not adequately explained by any of the above mechanisms. It has been reported[13] that after total glossectomy pain may be referred to the region of the tongue but without phantom sensation when a glossopharyngeal neuroma is present. The central mechanism proposed, involving reflex arcs in the spinal cord, would not apply in our case since sensory input from the face and tongue involves cranial nerves. The model of central biasing by the reticular formation would allow tonic inhibition to be decreased by loss of sensory input from the tongue, a small total area compared to a limb. However, the tongue is an organ rich in sensory receptors. Through an individual's life the tongue has been highly trained to perceive taste, temperature, texture, and sensation, and a clear image or model is formed. Thus, loss of the tongue may remove input similar to that observed after amputation of a limb.

Treatment of phantom pain remains a dilemma, and a long-lasting, consistently successful treatment is not known. Many treatments have been proposed: local anesthesia or hypertonic saline injection into the stump; nerve blocks; infiltration of trigger zones with local anesthetics; blocks of sympathetic ganglia; spinal anesthesia; continuous epidural anesthesia; rhizotomy; cordotomy; postcentral gyrectomy; frontal leucotomy; thalamotomy; transcutaneous nerve stimulation; distraction conditioning; hypnosis; psychotherapy; and antidepressants. Although each has been reported to be effective in individual cases, none is universally successful and the phantom pain often returns over the years. Further, although phantom pain may be eliminated, the phantom sensation often persists.

Sympathetic blockade or sympathectomy have continued to be advocated[6, 7, 14, 15] for treatment of phantom limb pain. Kallio[16] achieved approximately 50% transitory improvement in 69 patients treated with sympathectomy. However, only 10% had 4-year relief. Sympathectomy may also relieve phantom pain after digital amputation.[17] A trial of sympathetic blockade is recommended if there is evidence of abnormal vasomotor activity in a limb stump.[6, 17]

Sympathetic blockade through the stellate ganglion was selected in our patient because of the similarity of the burning facial pain to causalgia. The additional relief of the phantom tongue pain was unexpected. Five stellate ganglion blocks were performed according to our protocol for the management of causalgia. The resultant relief of phantom tongue pain without relief of the phantom tongue sensation is similar to the relief sometimes achieved following sympathetic blockade in patients with phantom limb pain.

Phantom tongue pain is an unusual occurrence following radical cancer surgery. In our patient, associated burning facial pain and hyperesthesia represented an atypical form of causalagia. Stellate ganglion block proved to be a safe and efficacious treatment for both the causalgia and the phantom tongue pain.

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Cardiovascular Effects of Bone Cement

The objective of this study was to determine the relationship between plasma concentrations of methyl methacrylate monomer and the cardiovascular disturbances observed during use of acrylic bone cement. Twenty-four anesthetized, paralyzed, and ventilated dogs were divided into three equal groups. Tritiated methyl methacrylate monomer was infused intravenously at rates of 0.05 and 0.1 ml/kg while the control group was untreated. Methyl methacrylate monomer plasma concentrations were determined by counting tritium activity in arterial blood samples. There were no significant cardiovascular changes in the 0.05 ml/kg group, in spite of a peak methyl methacrylate monomer blood concentration of 5.48 ± 0.89 mg/100 ml (mean ± SE). In the 0.1 ml/kg group significant changes included increases in cardiac output and pulmonary systolic and diastolic pressures and decreases in systolic and diastolic systemic arterial pressure and systemic peripheral resistance. Peak blood levels were 11.37 ± 0.74 mg/100 ml. The authors suggest that the blood levels of methyl methacrylate monomer required to produce cardiovascular change are far in excess of those likely to be encountered clinically. They question the postulate that circulating monomer is the sole causative factor of hemodynamic changes during clinical use of methyl methacrylate monomer. (*d'Hollander A, Monteny E, Hooghe L, et al: Cardiovascular effects of methyl methacrylate monomer. Surg Gynecol Obstet 149:61–64, 1979*)

Emergency Room Intubations

Forty-three consecutive patients requiring endotracheal intubation in an emergency room were studied prospectively to define the complications associated with intubation and the survival of these patients, and to evaluate emergency room policies. The indications for intubation were acute respiratory failure (ARF) in 22 patients and cardiopulmonary arrest (CPA) in 21 patients. Thirty-eight complications occurred in 24 of the 43 patients. The department or level of training of the intubator did not affect the rate of complications. Furthermore, specific complications did not influence survival. Seventeen patients survived, all in the ARF group. Age less than 40 years and admission $\mathrm{Pa}_{\mathrm{O}_2}$ >40 mm Hg also were associated with increased survival. The authors conclude that the complication rate of emergency room intubations is high and would not appear to be lowered by limiting intubations to physicians from specific departments or with certain levels of training. The underlying diagnosis and condition on admission to the emergency room appear to be more important factors relating to survival than complications during intubation. (*Taryle DA, Chandler JE, Good JT Jr, et al: Emergency room intubations—complications and survival. Chest 75:541–543, 1979*)

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ANESTH ANALG
58:439, 1979

Transfusion Anemia

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Frederic A. Berry, Jr, MD†

Management of intraoperative blood loss and replacement in small infants is often difficult for a variety of reasons. Most clinicians use a combination of factors in determining blood replacement needs. Measured and visually estimated blood loss, trends in vital signs, the patient's response to blood and fluid replacement, and serial measurement of hematocrit all supply data to guide transfusion therapy. We report a case in which there was a progressive decline in intraoperative hematocrit to alarming levels despite vigorous blood replacement in excess of estimated blood loss in the presence of stable vital signs.

Case Report

A full term 2.8-kg male newborn appeared normal at birth but subsequently developed a massive metabolic acidosis due to an inborn error of tyrosine metabolism. Hospital treatment included constant infusion of 0.3 M THAM in an attempt to control the acidosis while diagnostic studies proceeded. At 8 days of age the infant developed diffuse intravascular coagulation and necrotizing enterocolitis; emergency laparotomy was scheduled. At this time, the infant was septic and in shock, with minimal urine output. After appropriate preoperative fluid resuscitation the infant was taken to the operating room, where a total colectomy was performed under anesthesia with ketamine, nitrous oxide, morphine, and pancuronium.

At the beginning of surgery, blood drawn for blood gas analysis showed a hematocrit of 37%. Transfusion of whole blood was begun with the start of surgery because of several factors: (1) previous poor condition of the infant, (2) the low hematocrit of 37% (normal hematocrit at this age is 50 to 54%), and (3) a projected blood loss exceeding 20% of the infant's estimated blood volume of 220 ml.

During the 1st hour of surgery, the patient received 55 ml of bank blood to replace an estimated blood loss of 30 ml. Hematocrit at this time was 32%. After an additional ½ hour, estimated blood loss and blood replacement both equaled 100 ml, and a new blood sample showed a hematocrit of 26%. The patient received no crystalloid during the surgery.

At this time, attention was directed to the two aliquots of bank blood, which were supplied from the blood bank by "splitting" a stored unit of whole blood into two auxillary bags linked to the collection bag by plastic tubing. The aliquot of blood being administered to the patient was found to have a hematocrit of 20%, while the unused bag of blood derived from the same unit of bank blood had a hematocrit of 48%. A third aliquot of the same blood had been transfused preoperatively.

Postoperatively, the patient received further transfusions, but eventually expired from acidosis, shock and intracerebral hemorrhage.

Discussion

This case represents a potential complication related to the practice of "splitting" a unit of bank blood into multiple packages to facilitate proper storage and efficient use of bank blood in small infants. This repackaging of bank blood allows an infant to receive several transfusions over a period of several days while avoiding wastage of bank blood and minimizing the infant's exposure to multiple donors. In this case, however, the original unit of blood presumably had settled in its storage bag and was inadequately mixed when redistributed into its auxillary bags for separate use.

This problem should be avoided by thorough mixing of the stored blood prior to and during its redistribution in multiple bags. However, the anesthesiologist should be alert to the possibility of an anemic aliquot of blood when a partial unit of blood is administered. In this case, the color difference in the two remaining blood bags was not appreciated due to the smaller volume of the anemic aliquot, which distended its container less and was initially felt to be visibly lighter in color only due to the narrowness of its transparent container.

This case illustrates the value of serial hematocrit determination in monitoring intraoperative blood loss and documents a source of potential error in administering split units of bank blood.

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Reprint requests to Dr. Berry.

letters TO THE EDITOR

Enflurane Vaporizer Accuracy with Nitrous Oxide Mixtures

To the Editor:

We read with interest the paper by Nawaf and Stoelting[1] concerning the Ēthrane vapor output of Ohio Ēthrane vaporizers with changes in carrier gas, especially with N_2O. According to the authors, regardless of total flow, the presence of 60% N_2O increased the enflurane concentration by 20 to 40% above the concentration measured when only oxygen was flowing through the vaporizer. The mechanism responsible for this effect was not discussed definitively by the authors. Their finding was in contrast to the results of Diaz[2] with halothane and to my findings (unpublished data).

Instead of a gas chromatograph, we used a mass spectrometer (Perkin-Elmer model 1100A) to obtain an accurate dynamic output of various vaporizers at a 10-cm distance from the vaporizer outlet and found an effect on vaporizer enflurane output opposite to that of Nawaf and Stoelting in the presence of nitrous oxide. The magnitude and duration of the observed reduction in enflurane concentration were related to the vaporizer dial setting, the concentration of nitrous oxide, and the total gas flow through the vaporizer. The higher the flow, the less the reduction and its duration; the lower the dial setting, the greater the reduction and its duration; and the greater the concentration of nitrous oxide, the greater the magnitude of the reduction.

As shown in Fig 1, with a new Ohio Ēthrane vaporizer at a 1% dial setting and at a total gas flow of 3000 ml/min, a flow of 100% oxygen was changed to 100% N_2O. This change resulted in an immediate although temporary reduction of vaporizer enflurane output, which reached a maximum of 50 to 60% and took approximately 10 minutes to return to the previous level.

When the enflurane level had again become stabilized (Fig 1), we changed the gas flow back from 3000 ml/min of N_2O (100%) to 3000 ml/min of O_2 (100%), without changing the dial setting of vaporizer. The tracing shows the very large increase in enflurane concentration that resulted. Depending on the dial setting and the total gas flow used, the vaporizer enflurane output was found to increase by 50 to 350% for periods of 5 minutes or longer. At higher dial settings and total gas flows, the height and duration of the rise became smaller; at higher concentrations of nitrous oxide, the rise was more pronounced.

Our data indicate, in agreement with Diaz,[2] that these changes are mainly related to the viscosity of the carrier gas. The size of the vaporizer chamber is related to the duration of the changes. When the previous carrier gas is being washed out of the vaporizer chamber by the new carrier gas, the flow distribution between the bypass and the chamber must return to normal for the vapor output to return to its original level. The direction of the change in enflurane output in this case is determined by the rel-

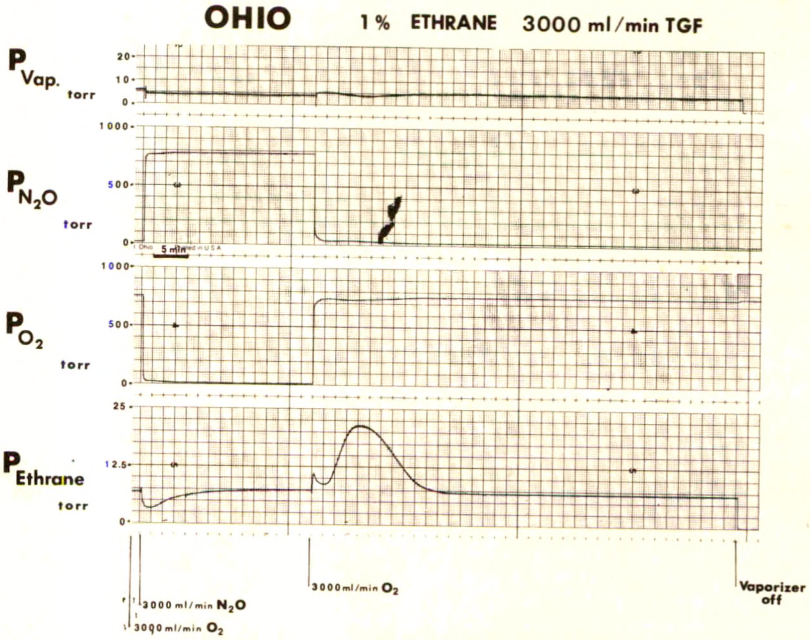

Fig 1. Tracing of continuous enflurane vapor output in relation to changes in carrier gas, at a distance of 10 cm from a new Ohio Ethrane vaporizer at 1% Ethrane setting. Measurements were made by mass spectrometer. Pressure was measured 10 cm proximal to the vaporizer (between oxygen or nitrous-oxide flow meter and vaporizer). Vaporizer output changes follow the change in carrier gas. When 100% oxygen is changed to 100% oxygen nitrous oxide, the changes takes several minutes to become complete, and a small concentration of oxygen continues to be put out by the vaporizer for some time; this period coincides with the change in enflurane vapor output. There was an increase in enflurane vapor output which reached approximately 300% for more than 5 minutes when the change was made from 100% nitrous oxide back to 100% oxygen as carrier gas.

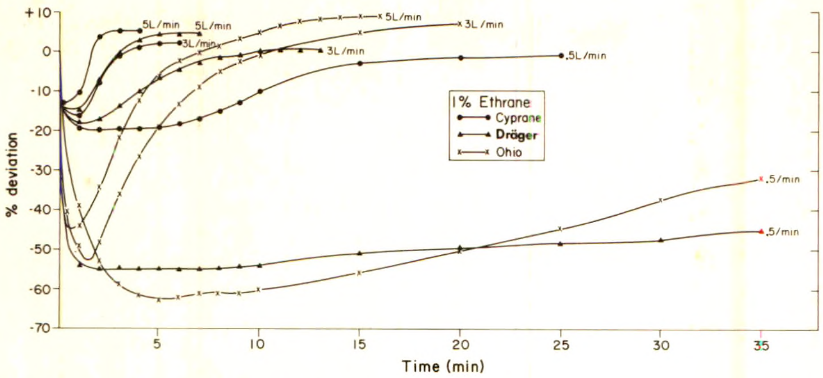

FIG 2. Change in enflurane output when carrier gas is changed from 100% oxygen to 100% nitrous oxide at flow settings of 5000 ml/min, 3000 ml/min, and 500 ml/min at 1% Ethrane setting, with Ohio, Cyprane, and Dräger Ethrane vaporizers. The Cyprane vaporizer showed the smallest changes and shortest duration at all three gas flows.

ative viscosities of oxygen and nitrous oxide (203.31 and 145.6 μP, respectively).

With vaporizers such as the Cyprane, Dräger, and Foregger, we observed similar effects, but with a lesser reduction in the enflurane concentration, as shown in Fig 2. A detailed report on these studies is being prepared.

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To the Editor

We recently reported that nitrous oxide increased the enflurane concentration delivered from calibrated Ethrane vaporizers.[1] Since publication of this report several investigators have informed us they are unable to duplicate these data. The communication from Lin emphasizes these discrepancies. In view of these conflicting observations, we have repeated our study using the conditions described in our original publication. We have discovered that identical enflurane concentrations produce a greater gas chromatograph peak height when the oxygen concentration of the sample is reduced by nitrous oxide. In our original study, this greater peak height response was erroneously assumed to represent increased enflurane concentrations delivered by the Ethrane vaporizer in the presence of nitrous oxide.

The most likely explanation for this spurious gas chromatograph response is the release of a contaminant from the gas chromatograph column (3% SE-30 on chromosorb W) at the temperature (130 C) and flows (hydrogen, 100 ml/min; helium, 35 ml/min; air, 300 ml/min) used. Apparently, this contaminant reacted with enflurane and resulted in a reproducible increase in peak height when nitrous oxide reduced the oxygen concentration of the analyzed sample. It should be emphasized that the reduced oxygen concentration and not the presence of nitrous oxide produced these greater peak height responses. Indeed, 100% nitrous oxide did not produce a gas chromatograph response.

Using the same flame ionization detector and column but at a lower column temperature (80 C) and gas flows (hydrogen, 80 ml/min; helium, 20 ml/min; air, 200 ml/min) we have observed that the same enflurane concentration produced identical peak heights with or without nitrous oxide. Enflurane concentrations at these gas chromatograph settings were measured using the same two Ethrane vaporizers originally studied. Flows through the vaporizer were either 5 L/min of oxygen or 3 L/min of nitrous oxide plus 2 L/min of oxygen. These data and corresponding data from the earlier study[1] are summarized in the Table.

TABLE
Flows Through Ethrane Vaporizers*

Vaporizer setting	Enflurane concentration (%)	
	5 L/min O_2	3 L/min N_2O-2 L/min O_2
.25	0.28 (0.38)	0.24 (0.41)
.50	0.57 (0.59)	0.49 (0.74)
1	1.06 (0.93)	0.96 (1.34)
2	2.01 (1.98)	1.82 (2.75)
3	3.23 (2.97)	3.09 (3.90)
4	4.01 (3.85)	4.16 (4.97)

* All values are averages from the same two Ethrane vaporizers. Values in parentheses suggesting increased enflurane concentrations in the presence of nitrous oxide are the erroneous values reported previously.[1]

It is apparent that nitrous oxide does not increase enflurane output from the two tested vaporizers. In fact, enflurane output may decrease slightly (also observed by Lin) when nitrous oxide is present in the carrier gas flows. This is consistent with the Ethrane vaporizer construction which would result in less gas flow through the vaporizing chamber when carrier gas viscosity was reduced by nitrous oxide (Personal communication, Ohio Medical Products).

We conclude that nitrous oxide will not significantly increase nitrous oxide output from calibrated Ethrane vaporizers (Ohio Medical Products and Cyprane Ltd). Therefore, use of these vaporizers should not be altered based on the concern that increased enflurane output occurs when nitrous oxide is present in the gases flowing through the vaporizer.

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Purity of USP Medical Oxygen

To the Editor:

Recently we had occasion to assay samples of medical oxygen from two major manufacturers. We had suspected contamination by a hydrocarbon on the basis of an unexpected gas chromatograph peak, but we were unable to verify this. Our review of the United States Pharmacopeia standards for medical oxygen[1] has caused us to question their adequacy.

Medical grade oxygen is required to be 99% pure. Of the remaining 1% (10,000 ppm), not more than 300 ppm of carbon dioxide, 10 ppm of carbon monoxide, and 5 ppm of oxides of nitrogen can be present. No other contaminants are specifically excluded from the other 9,685 ppm. Thus, the following hypothetical mixture would meet present USP standards:

Compound	%
O_2	99.40
HCN	0.10 (1,000 ppm)
Benzene	0.25 (2,500 ppm)
CCl_4	0.25 (2,500 ppm)
Total	100.00

These concentrations of cyanide and benzene are 100 times the threshold limit value (TLV) of each, the amount specified by the American Conference of Governmental Industrial Hygienists as the maximum allowable concentration for human exposure during any 8 hour period (2). The TLV for carbon tetrachloride is 100 ppm so it is exceeded 25-fold in the above example.

Aside from chemical tests for CO_2, CO, and nitrogen oxides, the only test required by USP is that the oxygen have "no appreciable odor." This test is less sensitive than the old Welsh bioassay of the canary in the coal mine. Surely we have progressed to the stage where readily available instrumentation should be used to spot check the purity of the therapeutic agent used more often than any other in the care of the critically ill patient. Until we are able to spot check the purity of medical oxygen accurately and simply, or until USP standards for medical oxygen are more closely defined, anesthesiologists should bear in mind the possibility, however remote, that USP medical oxygen may contain potentially dangerous compounds.

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Organization of Neonatal Resuscitation Equipment

To the Editor:

The delivery room is a common setting for neonatal cardiopulmonary resuscitation. Many delivery services are not organized or equipped to handle newborn resuscitation due to the relative infrequency of its occurrence and staffing limitations. An orderly arrangement of equipment and assignment of tasks may increase the efficiency of the staff and shorten the time needed to initiate resuscitation. We have developed a resuscitation tray organized so that all supplies for endotracheal intubation, umbilical vessel catheterization, and medication of a depressed neonate are easily accessible.

The tray (Figure) is composed of three units: one for endotracheal intubation (53 x 21 x 4 cm), one for medication (53 x 13 x 4 cm), and one for umbilical catheterization (53 x 30 x 4 cm). Each unit is made of polyester urethane foam and has a hard back-

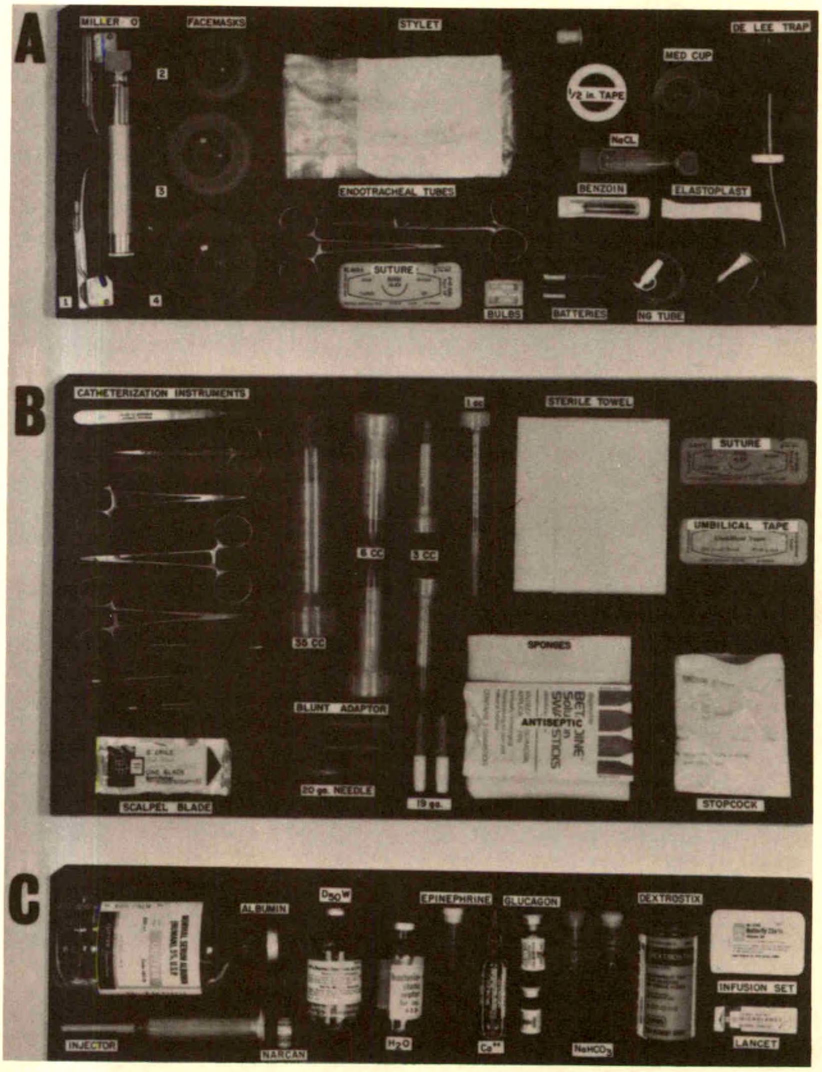

FIGURE. Neonatal resuscitation tray: A, intubation; B, umbilical catheterization; C, medication sections.

ing. The material can be modified depending on instrument and medication preference and availability. The intubation and umbilical catheterization materials may be individually wrapped in plastic and gas-sterilized with ethylene oxide. Sterile gloves and 5 and 3.5 French radiopaque catheters are enclosed in the umbilical catheterization unit. An inventory of the materials comprising each tray is available upon request.

Whereas this tray has been used primarily in the delivery room, it is also adaptable for use in the nursery and neonatal intensive care unit. Although in our unit the three sections of the tray (intubation, catheterization, and medication) are utilized separately, others might find it more convenient to package the three sections as a single tray. We wrap the trays in clear plastic prior to gas sterilization. With transparent wrapping, it is possible to locate each component of the tray, even before the seal is broken.

We believe that the development of this tray has shortened the time necessary to set up resuscitative equipment, has improved personnel organization, and has heightened efficiency of resuscitation. We also use this tray as a teaching tool in the orientation of physicians, nurses, and paraprofessionals to neonatal resuscitation. Finally, the tray has reduced the problem of missing equipment and inadequate restocking of supplies for neonatal resuscitation.

At the completion of each resuscitation, the respiratory therapist cleans each piece of nondisposable equipment, restocks all disposable items, and places them in their respective cut-outs according to a diagram before the tray is wrapped for gas sterilization.

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Medical Student Views of Anesthesiology

To the Editor:

The article by Levin, Friedman, and Scott, "Anesthesiology and the Graduating Medical Student: A National Survey," (Anesth Analg *58:* 201–207, 1979) is challenging and impartial. The authors are to be congratulated.

It makes the point that "graduating medical students see anesthesiology's lack of relevance to primary care as a major reason for not exploring a career in anesthesiology."

The authors contend that this opinion cannot be changed. I suggest that "lack of relevance to primary care" can and should be manipulated in the following manner whenever teaching students: (A) Admit that anesthesiology does indeed lack relevance to primary care. (B) Explain why in the following way:

1. Much of medicine is not primary care. And it may be said, perhaps flippantly, that much of primary care is irrelevant to the individual's needs or complaints.

2. Anesthesiology provides an array of pharmacologic techniques which though not often used in primary care situations are of major value both to patients during surgery and to patients who are critically ill.

3. Anesthesiology has become mechanized to a high degree. Anesthesiologists should be happy that their work is done by machines in accordance with the ideal of supervisory automation. Boredom may ensue, but automation is a fact of life. One should be grateful that chemistry, engineering, and research have helped patients and physicians as much as they have. Besides, there are still many opportunities in clinical anesthesia for handing out equally valuable smiles and kind words.

4. Primary care situations often result in a team effort to resolve serious problems.

5. Medical school graduates who are psychologically equipped for the type of work represented by anesthesiology should not feel inferior, bored or degraded. As the French say: "Il n'y a pas de sot métier, il n'y a que de sottes gens." (There are no silly occupations, only silly people.)

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Intravascular Migration of Epidural Catheters

To the Editor:

We do not feel that the recommendation of Ravindran, Albrecht, and McKay (Anesth Analg *58:*252–253, 1979) that the injection of a small volume test dose of local anesthetic through an epidural catheter is sufficient to detect intravenous cannulation and to prevent the resulting and dangerous central nervous system and cardiovascular toxicity. Two years ago on this obstetrical unit a 17-year-old healthy parturient experienced a severe convulsion under circumstances almost identical to those reported by Ravindran et al. The main difference was that the convulsions were followed immediately by ventricular tachycardia and then fibrillation. Defibrillation was necessary to restore normal rhythm. The following precautions to avoid future recurrences were initiated. First, we inject the amount of bupivacaine for cesarean section or tubal ligation only through the epidural needle. If an epidural catheter has been previously placed for control of pain during labor it is removed and replaced with an epidural needle. Second, we inject 2 ml of local anesthetic through the epidural needle, wait two circulation times, inject a further 5 ml slowly, wait two circulation times, and repeat until the total volume is administered. Third, we maintain conversation with the patient by a series of questions. Change in the patient's sensorium is a valuable indication of inadvertent intravenous administration of local anesthetic. Fourth, we never perform epidural anesthesia for cesarean section or tubal ligation without attaching an EKG before the injection of the local anesthetic. Fifth, we replaced all 20-gauge epidural catheters with 19-gauge. To obtain perineal anesthesia during vaginal delivery we inject 3% chloroprocaine in repeated 5-ml doses.

In the past 2 years we have administered epidural anesthesia using a needle in 1057 cesarean sections and in 460 tubal ligations using 0.75% bupivacaine. We have not had a reaction due to intravenous injection using this technique. In 21 additional cases, injections were made through the catheter since this was already in place and we anticipated difficulty in reinserting the needle. Despite precautions we had one severe convulsion. In performing more than 2000 epidurals for vaginal delivery we have had no convulsions.

One of the dangers of injection through an epidural catheter, apart from kinking, may be related to Hagen-Poiseuille's law for laminar flow which states that flow rate is proportional to the fourth power of the diameter of a tube and inversely proportioned to the length of the tube and the viscosity of the fluid. With an epidural catheter the diameter is small and the length great. Because the viscosity of blood is 5 times that of the local anesthetic solution, it is thus more difficult to aspirate blood than to inject local anesthetic. Finally, use of a test dose is a precaution against subarachnoid injection and it takes at least 5 minutes for inadvertent spinal anesthesia to become apparent. The greater danger of intravenous injection can be detected in two circulation times.

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Memory Loss from Intravenous Diazepam

Memory consists of three successive stages: (1) storage, the encoding and registration of information; (2) retention, the maintenance of stored information; and (3) retrieval, the recovery of that information. A word recognition task was designed to determine the stage in memory affected by a single 10-mg intravenous injection of diazepam and the duration of the effect. Injection in three experimental subjects produced an anterograde amnesia for the 14- to 24-minute period immediately after injection. Memory loss resulted from impaired storage, the stage during which information is entered into memory. Retention and retrieval stages of memory were unaffected. This temporary amnesia may result from increased inhibition in the hippocampal system produced by diazepam, which shares many properties with the inhibitory neurotransmitter gamma-aminobutyric acid. (*Clark EO, Glanzer M, Turndorf H: The pattern of memory loss resulting from intravenously administered diazepam. Arch Neurol 36:296–300, 1979*)

Epidural Morphine

Recent work in animals has demonstrated that injection of minute doses of narcotic analgesics into the spinal subarachnoid space produces analgesia, painful stimuli being blocked by an action taking place exclusively in the spinal cord. Drugs injected into the epidural space reach the spinal cord. This report describes the results of the injection of 2 mg of morphine in 10 ml of 5% glucose or normal saline into the lumbar epidural space in eight patients, and the thoracic epidural space in two. All patients were suffering from severe acute or chronic pain. Within 3 minutes of the injection of morphine, all patients reported a reduction in pain. Analgesia was maximum in 10 to 15 minutes and lasted for 6 to 24 hours. Although the experimental design does not allow exclusion of a placebo effect, the suggestion that epidural morphine administration produces analgesia is an interesting extension of the previously published information in this area. (*Behar M, Olshwang D, Magora F, et al: Epidural morphine in treatment of pain. Lancet 1:527–528, 1979*)

book REVIEWS

International Symposium on Pain of Advanced Cancer—Advances in Pain Research and Therapy, edited by J. J. Bonica and V. Ventafridda, New York, Raven Press, 1979, 736 pp, $48.00.

This volume is a collection of selected papers presented at the International Symposium on Pain of Advanced Cancer held in Venice, Italy, May 24–27, 1978.

The text is divided into two parts. Part 1 deals with considerations relating to the extent of the problem of cancer pain management, its neurophysiologic and psychosocial contributions, and the resultant emotional and behavioral manifestations. Part 2 contains sections relating to specific forms of management; oncological, psychosocial techniques, and neurostimulative approaches. Also discussed in the section is the specific management of some frequently occurring pain syndromes.

While most of the chapters contain material reworked from previous publications, this is the first attempt to collate into a single volume current concepts of cancer pain management. Unlike the first volume of *Advances in Pain Research and Therapy*, this volume is well edited with chapters bridged without repetition or contradiction. Comments are well cross-referenced throughout. The editors, however, could have deleted the discussions at the end of various sections since these are generally unsubstantiated comments and add little to the material presented. The use of subheadings provides ready access to topics of interest when the book is used as a reference source.

Illustrations generally are well chosen and representative of the descriptive text. Most of the illustrations in the three chapters on nerve blocks, however, are reprinted from Bonica's *The Management of Pain* and the techniques described do not always correlate with the illustrations.

The chapter by Cicely Saunders on the hospice concept emphasizes that the skilled and experienced management of the dying patient is the critical factor, not the physical unit. The concept of sympathy, caring, and relief of pain can be carried out in the patient's home or general hospital as well as in the special unit.

The summations of the panelists discussing future needs in cancer pain management are thoughtful in defining goals and objectives. All impress the importance of careful research and evaluation of results.

This book is recommended for any physician dealing with cancer pain management and for the anesthesiologist who has been concerned over the failure of nerve blocks for prolonged pain relief.

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Anesthetic Management of the Patient with Cardiovascular Disease, edited by D. M. Philbin. Boston, Little, Brown and Co., 1979, 197 pp, $35.00.

The most recent volume of the International Anesthesiology Clinic's series has been primarily written by the members of the cardiac anesthesia section of the Department of Anesthesia, Massachusetts General Hospital. This group obviously has wide experience and expertise in managing seriously ill patients with cardiovascular disease. The editor, a senior member of that group, has chosen to co-author four of the eight chapters presumably in an attempt to achieve continuity. Nonetheless, there is the usual discrepancy in chapter quality that is common to multi-authored volumes.

Chapter 2 on the "Cardiovascular effects of neuromuscular blocking agents," Chapter 4 on "The anesthetic management of the patient with valvular heart disease" and Chapter 6 on "Anesthesia for peripheral vascular disease" are particularly strong. In an attempt at brevity, the first chapter ("The cardiovascular effects of anesthetics: an introduction") presents a number of inaccuracies. In particular, the attempt to tabulate these effects in Table 1 falls far short of the goal. The authors of the third chapter on cardiac arrhythmias have also presented too simplistic a discussion. For example there is no mention of the newer antiarrhythmic drugs which would have been particularly helpful for the practicing anesthesiologist. It is somewhat disconcerting to find that the classic reference for the effect of anesthetics on cardiac rhythm (Katz and Bigger) is listed in the wrong year. The chapter with the greatest problems is that on the anesthetic management of the patient with coronary artery disease. There are numerous typographical and reference errors (for instance the fentanyl and ketamine references are completely confused in the text). Although the concept of controlling the systolic blood pressure-heart rate product is mentioned in the anesthetic management section of the chapter, there is no preliminary discussion of this useful estimate of myocardial oxygen consumption in the epidemiology section. The most serious proofreading error is found on page 119 where the starting dose of sodium nitroprusside is listed as 0.1 *mg*/kg/min instead of 0.1 *mcg*/kg/min. Chapter 8 on intraoperative monitoring is mistitled. Eleven of the 14 pages are devoted to the placement and management of pulmonary artery catheters. There is no mention of the increased morbidity from the use of larger sized radial artery cannulae and no description of an adaptation of the standard three-lead operating room electrocardiograph to monitor the precordium. Both would have been useful. The last chapter on deliberate hypotension is disappointing, particularly in view of the extensive experience of the author. Several important references are omitted. A substantial portion of this discussion revolves around 5-year-old abstracts as yet unpublished. The table listing the indication for controlled hypotension is poorly organized and repetitious. Finally there are several unsupported generalizations: "For all practical purposes we have accepted as satisfactory that pressure at which bleeding appears to be minimal." This can hardly be accepted as an objective criterion for the control of arterial pressure; and "A progressive decrease in myocardial O_2 demand (MVO_2) was reported by Fahmy and Laver (reference 5) as gauged by the heart rate-systolic arterial pressure product during anesthesia with deliberate hypotension, the suggestion being that the lessened coronary perfusion may be adequate during induced hypotension." Without objective measurement of the adequacy of coronary perfusion the fact that an estimate of myocardial oxygen consumption decreases in no way substantiates such a statement. Finally the current controversy concerning the usefulness of sodium nitroprusside vs nitroglycerin is barely touched upon. The strongest point in the chapter is the discussion of the contraindications to and requirements for deliberate hypotension.

In summary, the book is disappointing. More careful proofreading and fewer generalizations about the effects of drugs would have made the volume a much greater contribution toward the anesthetic care of patients with cardiovascular disease.

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Cardiovascular Physiology for Anesthesiologists, by R. J. Gordon, M. B. Ravin, and G. R. Daicoff. Springfield, Charles C Thomas, 1979, 209 pp, $19.75.

Mathematics and physics do not rank high on the usual physician's list of avocations. Thus it was with no small dismay that I encountered the expression:

$$A(\text{area}) = \int_{AT}^{AT=PT} C\,dt\,(\text{mg}\cdot\text{sec/l})$$

on page 13! I went back to the title page and discovered that, although the title did say the book was "for anesthesiologists," one of the authors is a professor of engineering!

Having promised to read the book in its entirety, I plowed on (by this time despairing of obtaining anything I could understand). To my surprise, I found rigorous explanations of the various methods of cardiac output determinations, and I actually understood most of them. The next chapter, on blood rheology, introduced concepts of shear, stress, strain, as they relate to blood. I had been vaguely aware that hemodilution, for example, results in a fluid which ought to be "thinner," and ought to "move around easier" in the vessels. Chapter 2 sets these difficult concepts into terms which can, in fact, be comprehended by at least this "dumb clinician."

Wondering what they would hit me with next, I gained interest in the book and it gained momentum and readability. Guyton's concepts of venous return curves and their importance in determining cardiac function are well explained, with pertinent examples.

The discussion on the coronary circulation is excellent. The authors carefully build a well-referenced case to explain why subendocardial blood flow is in greatest jeopardy, and why heart rate control is so crucial in avoiding an area of ischemia during anesthesia and surgery.

Although elements of more "classic" cardiovascular physiology are to be found in this book, the authors do not dwell upon those that have not proved particularly useful to clinicians, such as V_{max}. The authors chose instead a careful and extensive discussion of intramyocardial pressure distribution, and ways of clinically assuring maintenance of subendocardial flow and avoidance of undesirable supply-demand ratios.

The later chapters, on EKG interpretation, and anesthesia for correction of congenital heart disease, are in a much more "how I do it" style. They are written in the manner to which clinicians have become accustomed. Unfortunately, after the nicely sophisticated earlier parts, these chapters are a letdown. I was hoping for a detailed discussion of the effects of the obviously altered blood rheology on cardiovascular function in patients with congenital heart disease, since I had invested time in studying that subject earlier. Instead, we are told that, based on "previously discussed considerations regarding blood rheology" (page 188) we should try for a 25% hematocrit during bypass for repair of congenital heart disease.

Still, perhaps this book serves to point out a major weakness in medicine, namely our lack of appreciation for and understanding of the pertinent physical sciences. We probably could learn much from engineers and physicists. Overall, I enjoyed the book very much, and, although it was sometimes painful, I learned a lot. It is decidedly *not* a conventional CV physiology book! I can recommend it without reservation to those who regularly do cardiovascular anesthesia, and those who do related research. Anesthesia residents (hopefully nearer than I to physics and math) will also find it useful. Perhaps such an "unconventional" engineering approach is sorely needed.

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Respiratory Pharmacology and Therapeutics, by I. Ziment, Philadelphia, W B Saunders Co, 1978, 519 pp, $29.50.

The subject of respiratory pharmacology is badly in need of a comprehensive text to provide concise information for the wide variety of personnel involved in delivering respiratory care. This hardbound book by Dr Ziment attempts to do just that. The chapters are arranged logically, beginning with general information on respiratory drug pharmacology and aerosol therapy. The history and development of inhalation drugs is also presented in this chapter. The structure, production, and movement of respiratory tract secretions in health and disease are discussed in some detail in the next chapter. Each agent or drug that affects respiratory tract secretions is classified according to its method of administration. Attention is paid to details that are both practical and useful. For instance, dosage of each drug is followed by a recommendation and the reasons for the recommendation.

The section on bronchospasm is extensive and quite helpful. In this section the anatomy, physiology, and biochemistry of bronchospasm are discussed. The pharmacology and therapeutic aspects of sympathomimetic agents, phosphodiesterase inhibitors, corticosteroids, and cromolyn sodium are covered in four well written, well organized chapters. The scope of these chapters is admirable, and they contain much useful information. Antitussive agents, cold medicines, and mucosal decongestants are presented in detail. Antimicrobial and antifungal agents used in the treatment of respiratory infections are also presented. Although not specifically relevant, there is a review of the application of each antibiotic in the treatment of infections of the respiratory tract by specific organism.

Respiratory stimulants and depressants are presented in another chapter. Trivial as well as traditional drugs are included, and the author discusses the controversial place of the respiratory stimulants in patient management. A bibliography sufficient for independent pursuit of this topic is provided. A small part of this chapter is devoted to paralyzing agents, with only rudimentary discussion of classification and indications. The practical aspects of muscle relaxants, their dangers and contraindications are not well discussed. Local anesthetic pharmacology is adequately reviewed in the next chapter as well as that of other agents used in pulmonary diagnostic studies. Oxygen transport and hypoxia are briefly discussed in the subsequent chapter. The section on administration of oxygen is poorly referenced and consists mainly of the author's opinion or descriptions of his general routine patient care. The last section of the book provides some insight into the costs of formulations of various respiratory drugs.

In general, the content is up-to-date and informative. The tables (more than 300) are uniformly excellent and add much to the overall appeal of the book. For the clinician interested in respiratory therapy, who is looking for a reference source, this book will only partially satisfy that need. On the other hand, I feel it will be a very useful addition to the library of every respiratory therapy department.

Bahman Venus, MD
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BOOKS RECEIVED

Cardiovascular Function Principles and Applications, by F. L. Abel and E. P. McCutcheon, Boston, Little, Brown and Co., 1979, 424 pp, $35.00.

Clinical Simulations for Respiratory Care, by D. C. Assmann, S. J. Hixon, and R. M. Kacmarek, Chicago, Yearbook Medical Publishers, 1979, 175 pp, $22.50.

Mechanisms of Pain and Analgesic Compounds, edited by R. F. Beers and E. G. Bassett, New York, Raven Press, 1979, 510 pp, $39.50.

Mode of Action of Autonomic Drugs, by B. D. Bhagat, Flushing, NY, Graceway Publishing Co., 1979, 170 pp, $21.50.

Jamieson and Kay's Textbook of Surgical Physiology, by I. M. Ledingham and C. MacKay, New York, Churchill Livingstone, 1977, 381 pp, $47.50.

Pediatric Respiratory Therapy, 2nd edition, by M. D. Lough, C. F. Doershuk, and R. C. Stern, Chicago, Yearbook Medical Publishers, 1979, 313 pp, $18.95.

Lecture Notes on Anesthetics, by J. N. Lunn, London, Blackwell Scientific Publications, 1979, 170 pp, $9.95.

Management of the Patient-Ventilator System: A Team Approach, by K. V. Martz, J. Joiner, and R. M. Shepherd, St. Louis, CV Mosby Co, 1979, 254 pp, $9.95.

Clinical Management of Mother and Newborn, by G. F. Marx, New York, Springer-Verlag, 1979, 274 pp, $29.80.

Monitoring Cerebral Function, by P. F. Prior, Philadelphia, Lippincott/Harper, 1979, 366 pp, $30.00.

Coronary Heart Surgery, edited by H. Roskamm and M. Schmuziger, New York, Springer-Verlag, 1979, 394 pp, $42.90.

Pharmacology of Respiratory Therapy Medications, by M. J. Strauch, Chicago, Yearbook Medical Publishers, 1979, 249 pp, $14.95.

Management of Acute Intracranial Disasters, by R. V. Trubuhovich, Boston, Little, Brown and Co., 1979, 448 pp, $35.00.

A Guide for Authors

Manuscripts should be sent to:
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Symbols. Define all symbols when first used. Respiratory symbols must follow Pappenheimer J, et al: Standardization of definitions and symbols in respiratory physiology. Fed Proc 9:602–605, 1950.

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Examples:

Periodicals

Moore DC, Mather LE, Bridenbaugh LD, et al: Arterial and venous plasma levels of bupivacaine following peripheral nerve blocks. Anesth Analg 55:763–768, 1976

Munson ES, Embro WJ: Enflurane, isoflurane, and halothane and isolated human uterine muscle. Anesthesiology 46:11–14, 1977

Book

Avery MA, Fletcher BD: The Lung and Its Disorders in the Newborn Infant. Third edition. Philadelphia, WB Saunders Co, 1974, pp 54–58

Chapter in Edited Book

Phillips OC, Capizzi LS: Anesthesia mortality, in Public Health Aspects of Critical Care Medicine and Anesthesiology. Edited by P Safer. Philadelphia, FA Davis Co, 1974, pp 219–224

Illustrations. Include one complete set of illustrations with each copy of the manuscript. Number illustrations in order of citation. On a label on the back, give figure number, first author's name, and arrow indicating top of figure.

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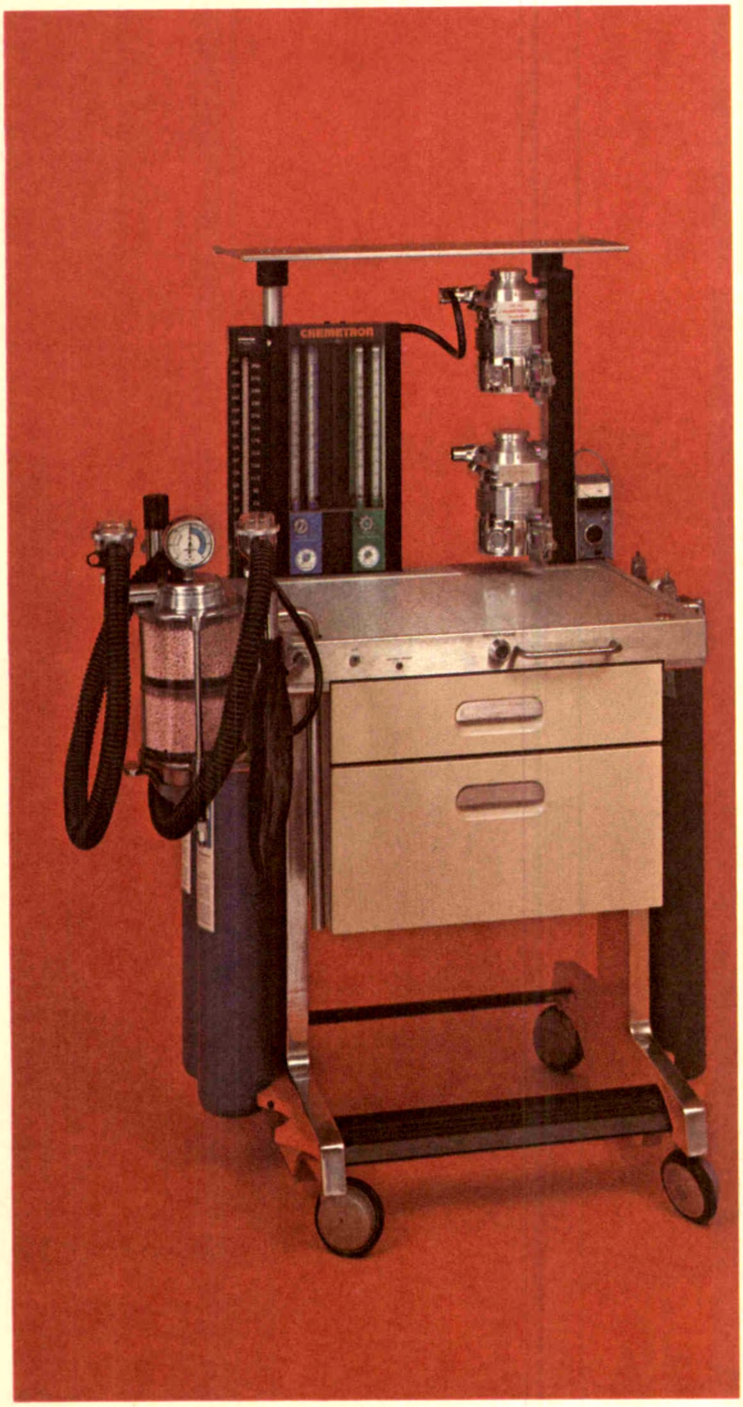

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References: 1. Brown, B.R., and Sipes, I.G.: Commentary-Biotransformation and hepatotoxicity of halothane, Biochem. Pharmacol. 26:2091, 1977. 2. Bunker, J.P., *et al:* The National Halothane Study, Washington, D.C. Government Printing Office, 1969.

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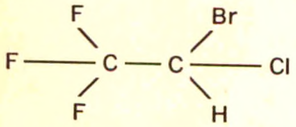

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FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE (halothane, U.S.P.) is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE (halothane, U.S.P.) has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

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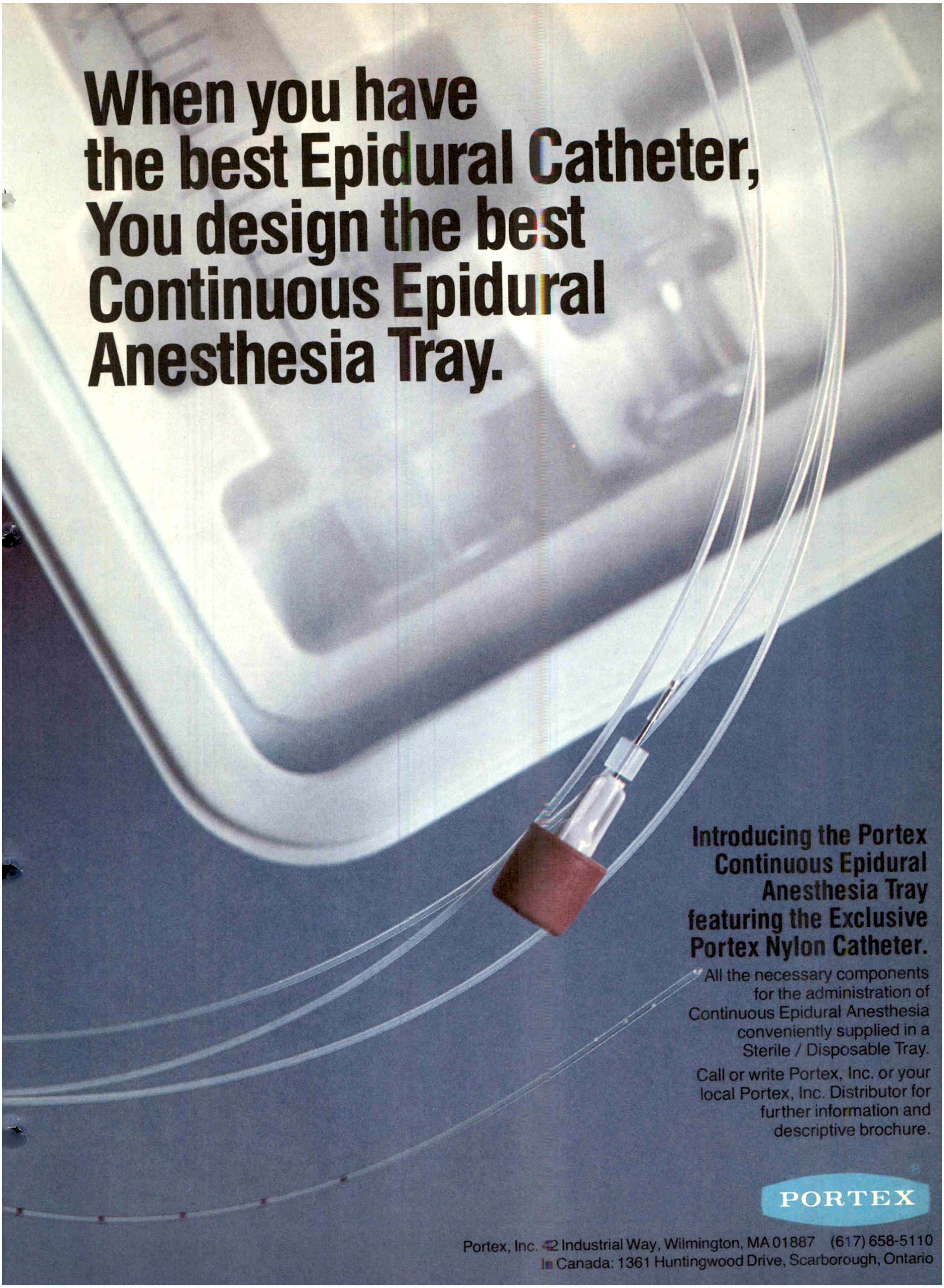

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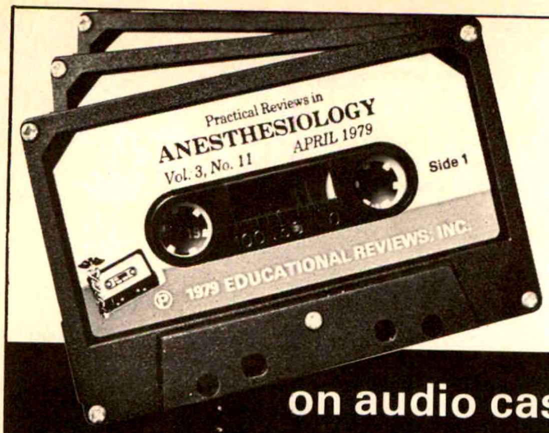

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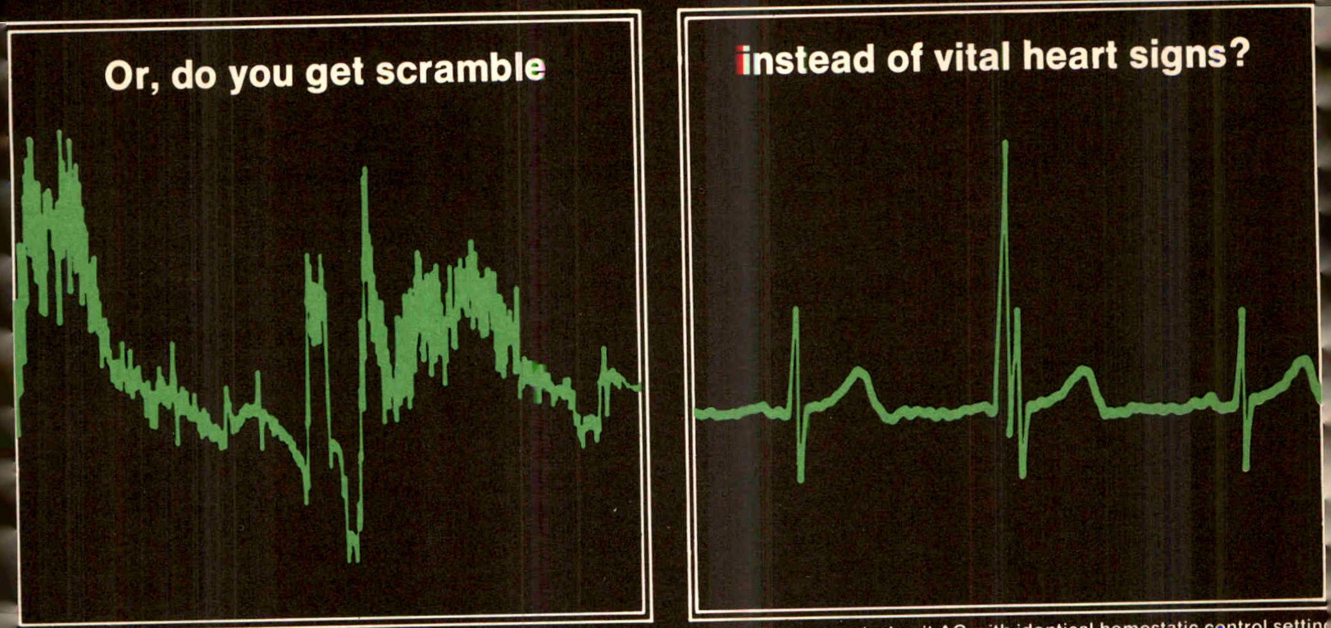
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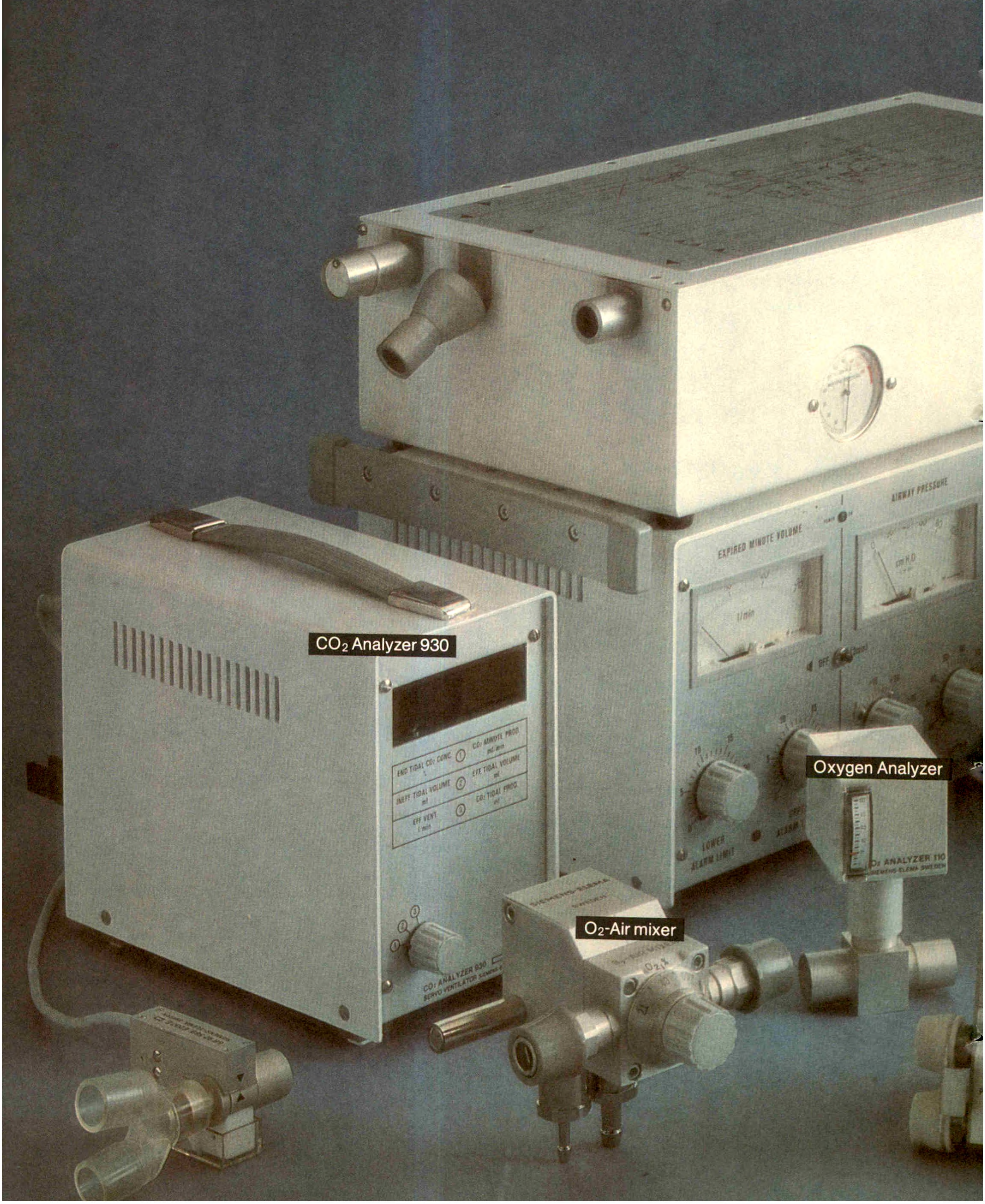

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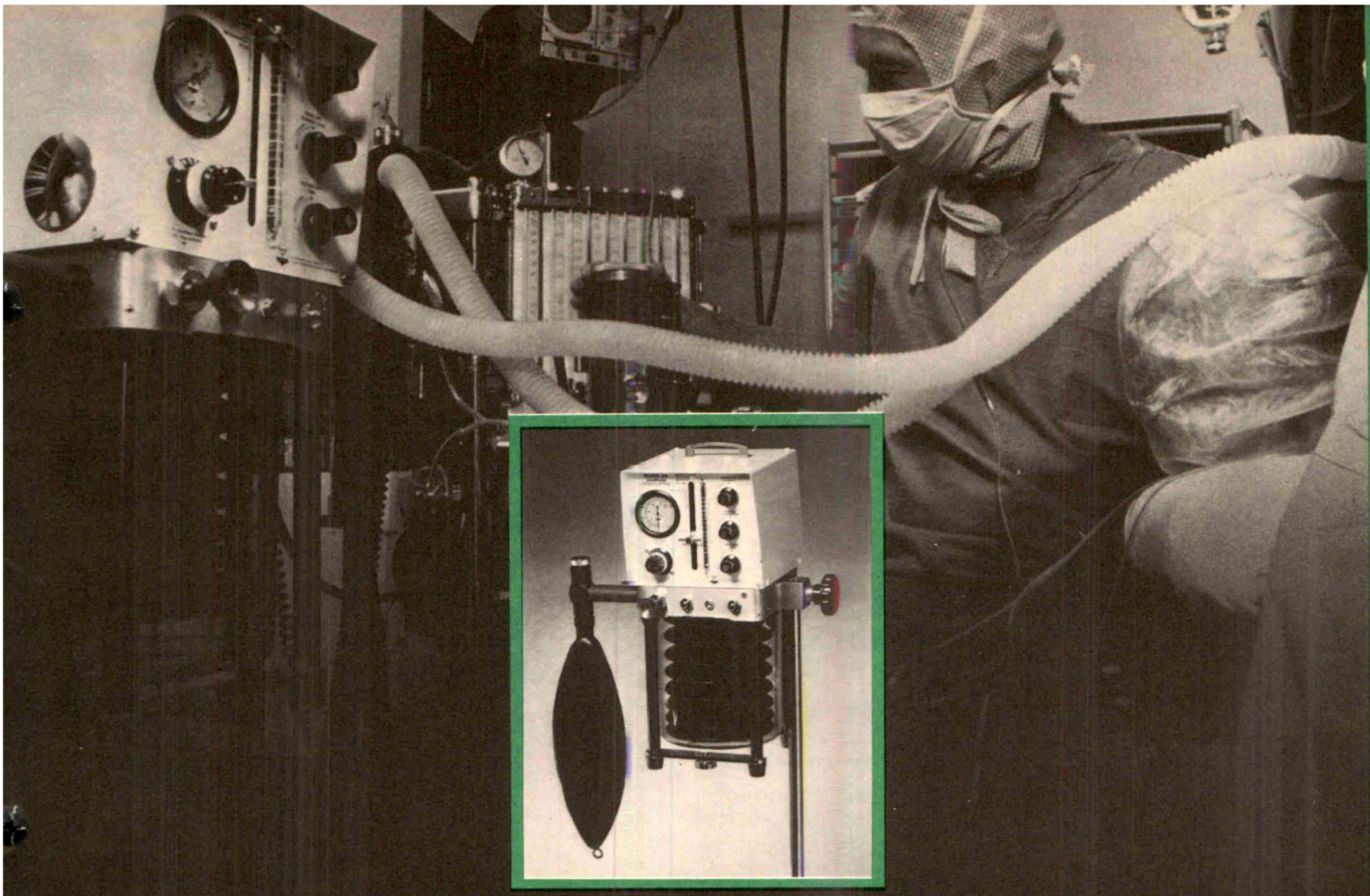

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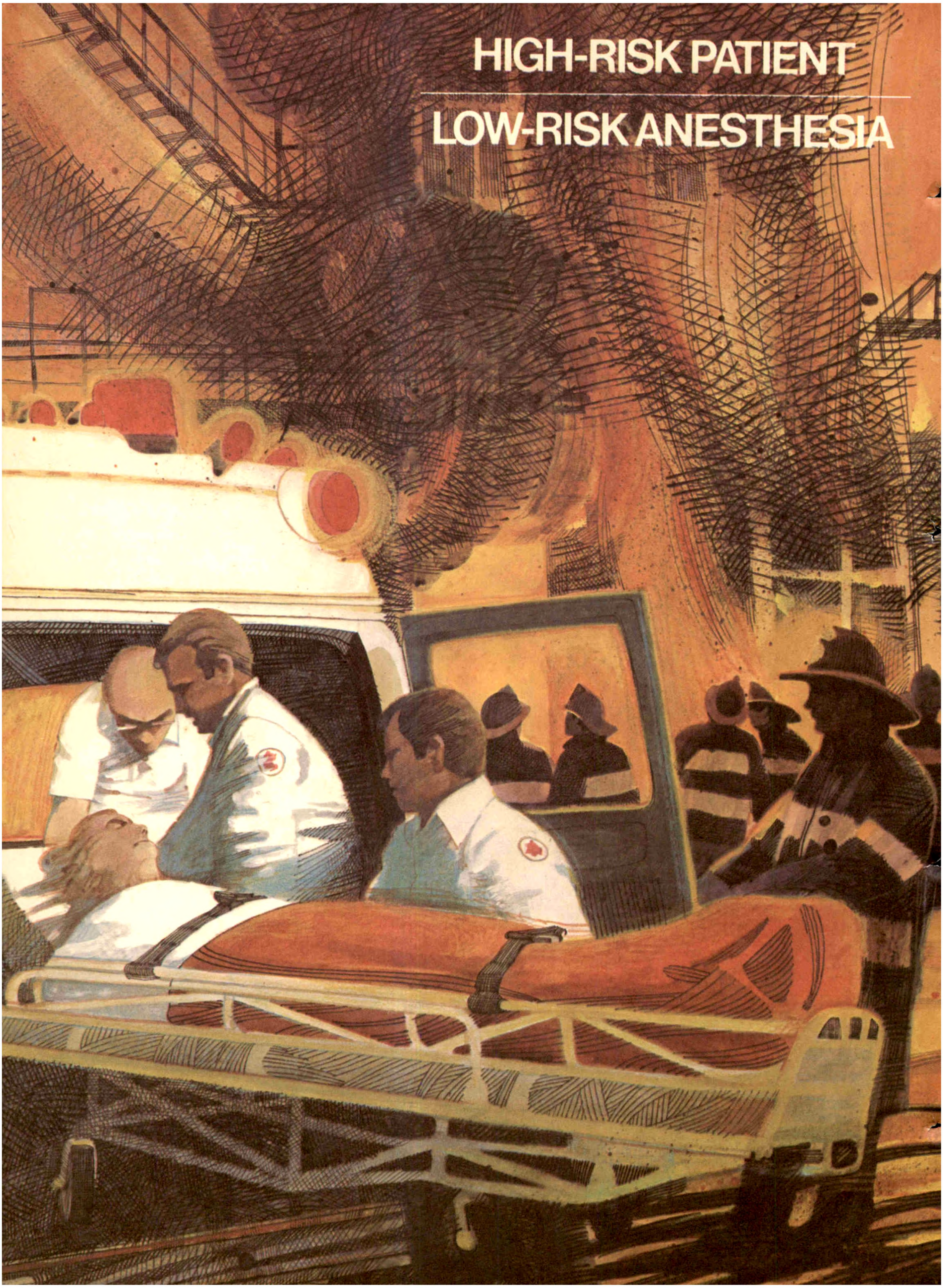
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THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA-SHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemcially incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy: Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. **The incidence of emergence reactions may be reduced** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

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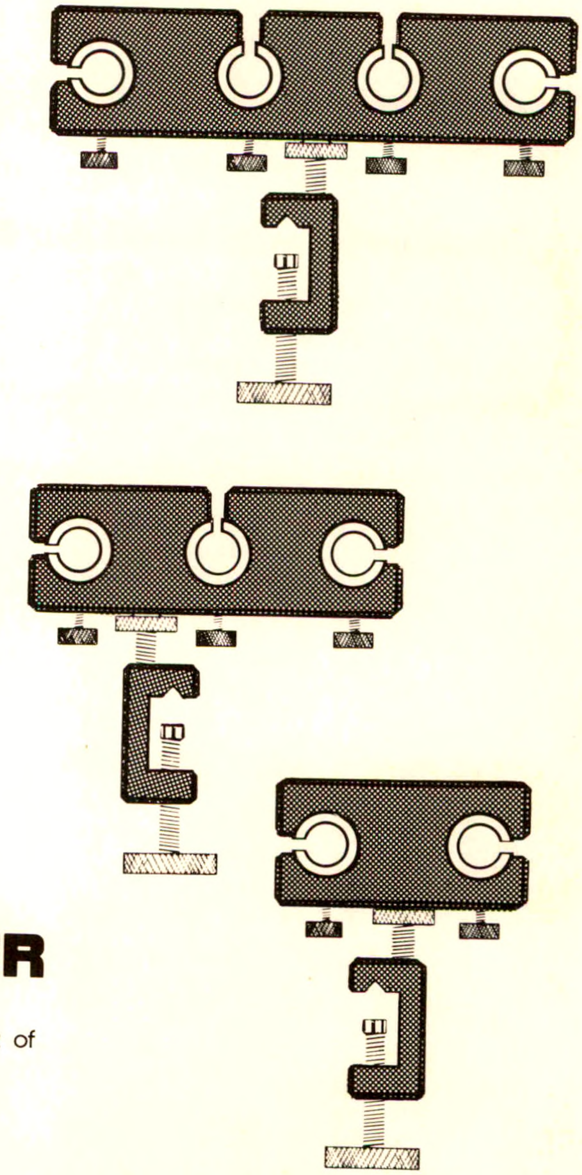

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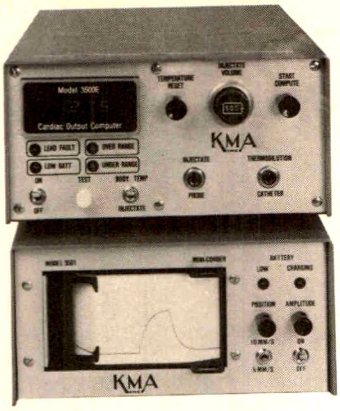

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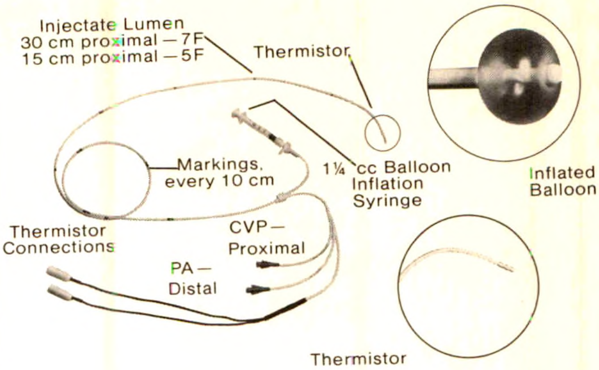

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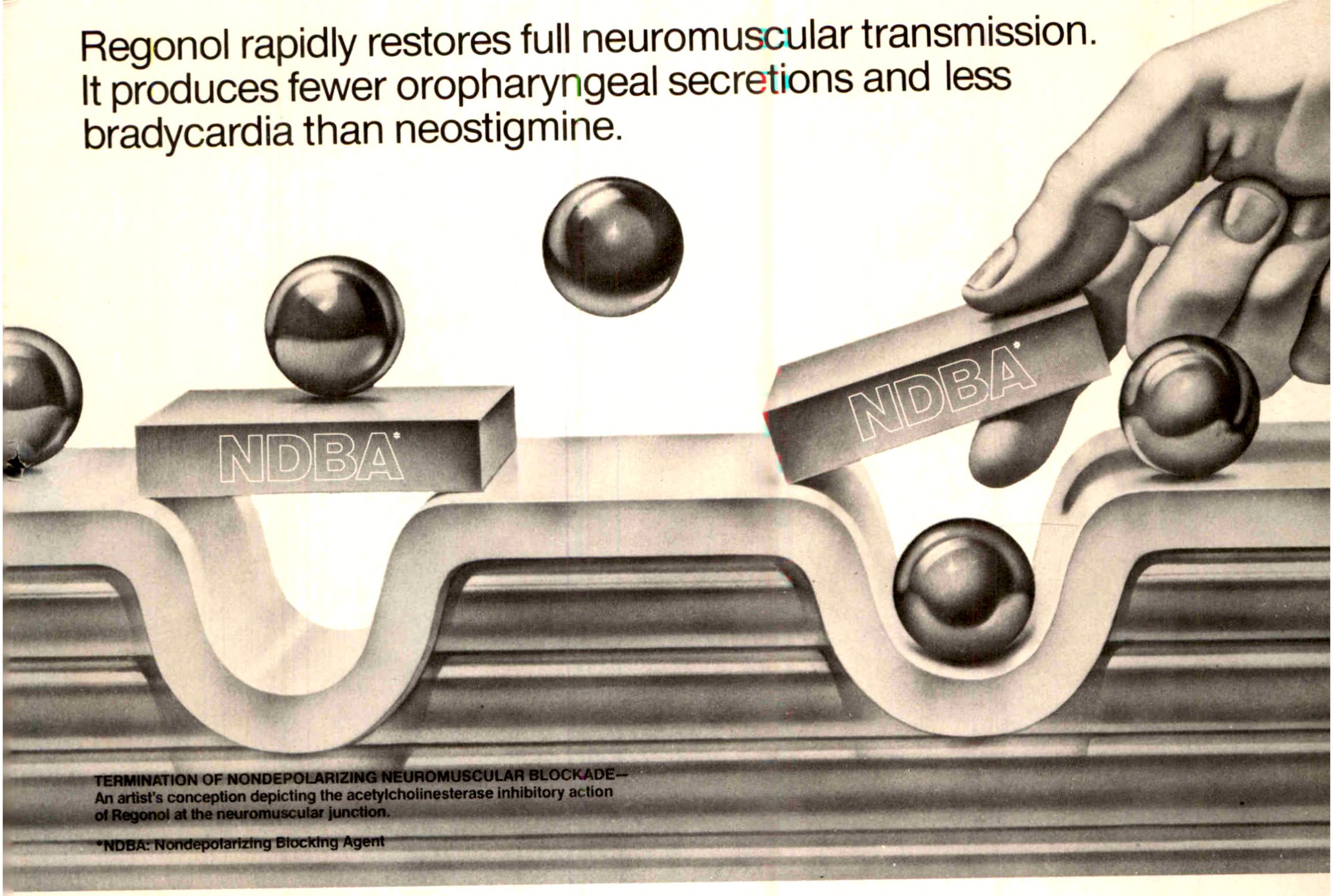

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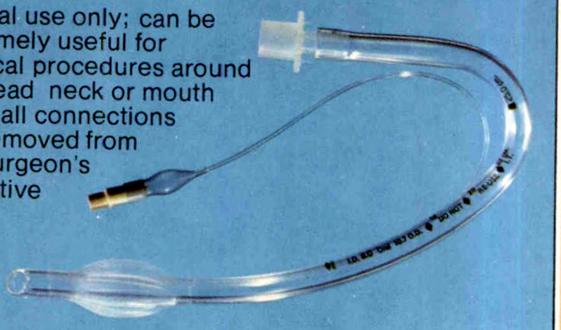

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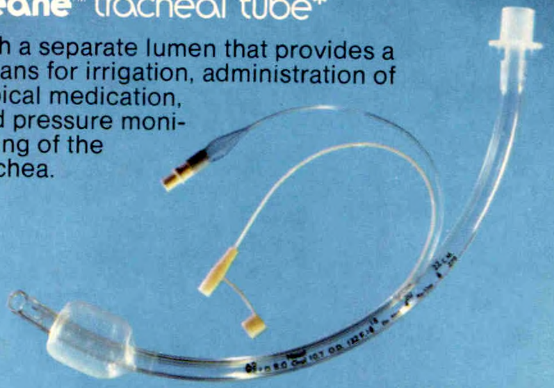

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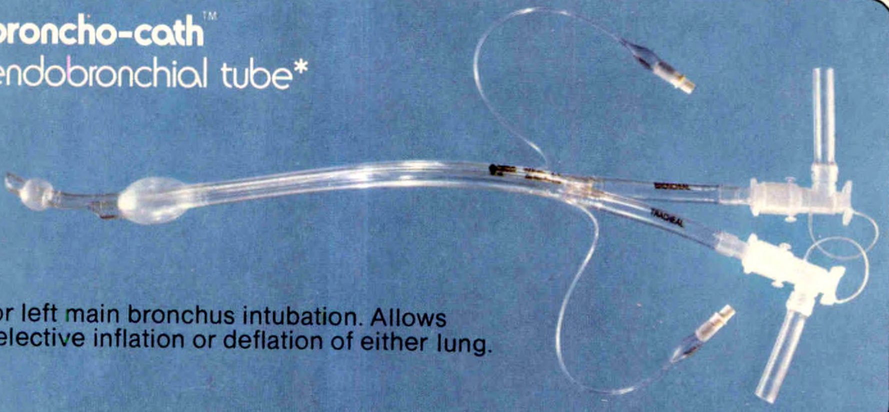

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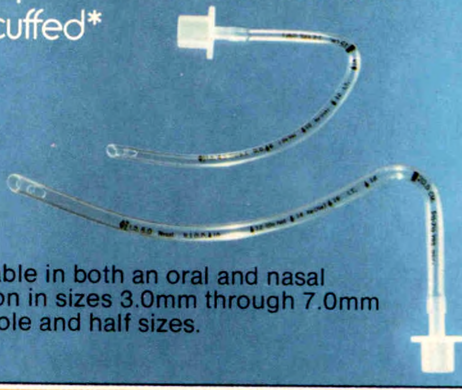

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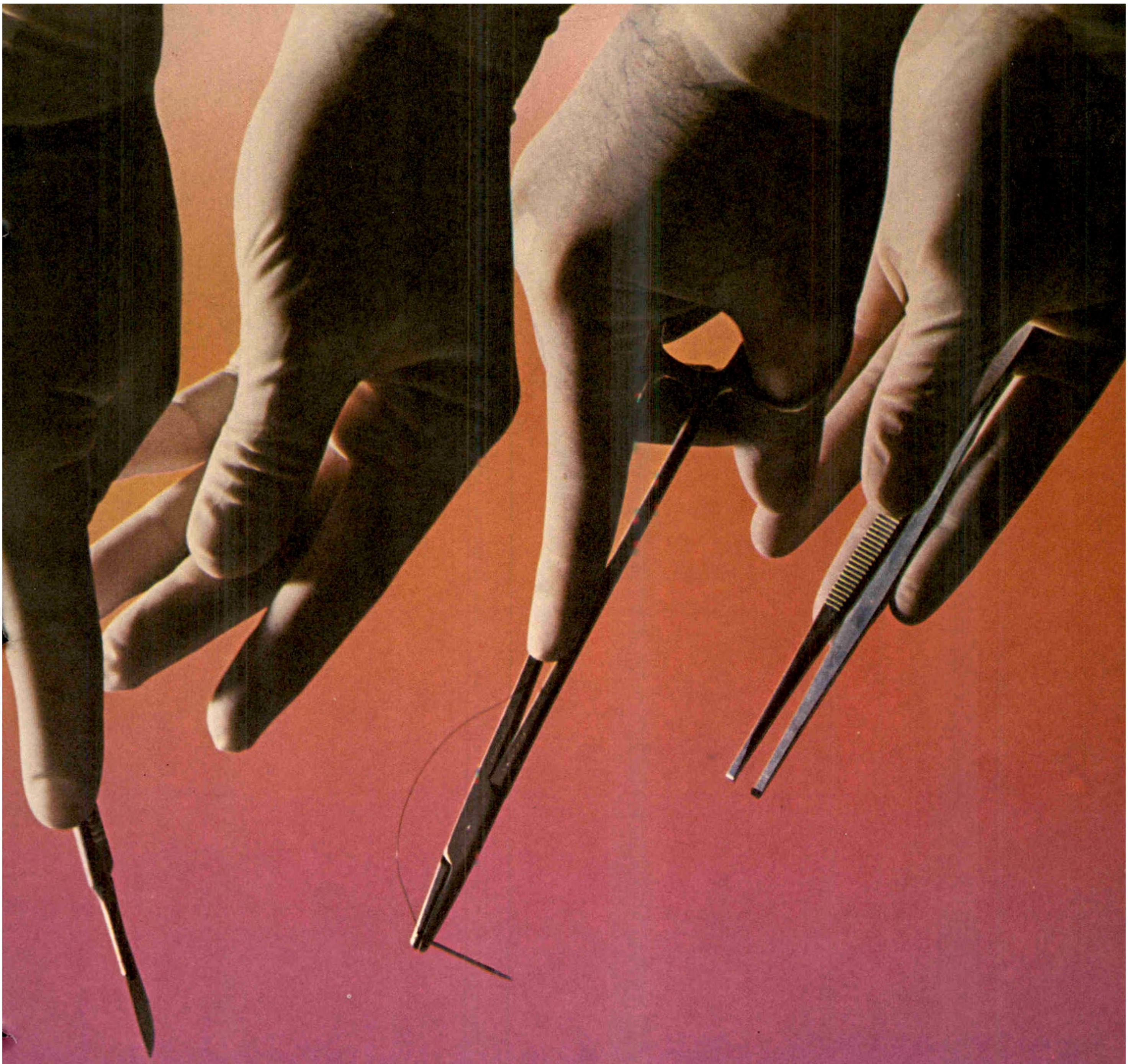
Beginning
with intubation,
Proceeding
through surgery,
Until closure
Proceed with



Pavulon facilitates intubation and provides safe, neuromuscular blockade.

Histamine release and ganglionic blockade are rarely, if ever, seen[1].

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pancuronium bromide

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Until closure

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pancuronium bromide

The clinically proven nondepolarizing muscle relaxant

Brief Summary (Please consult full package insert, enclosed in every package, before using Pavulon).

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

Reference:
1. Stanley and Liu. Anesth Analg 56 669, 1977

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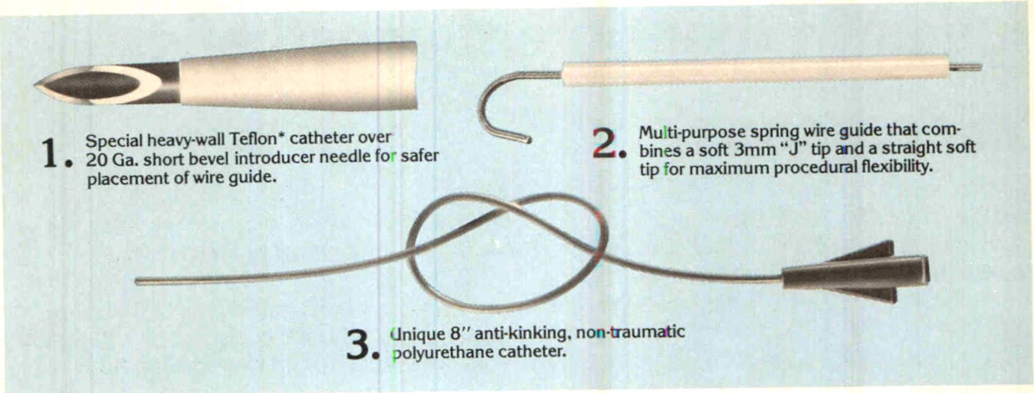
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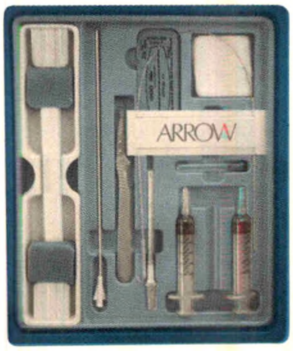

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Ēthrane® (enflurane)

Anesthetists are now using Ēthrane® (enflurane) more often than any other potent anesthetic.

Their reasons?

- **Stability of heart rhythm**
  A noteworthy feature of anesthesia with Ēthrane (enflurane) is stability of heart rhythm[1].
- **Compatibility with epinephrine**
  The compatibility of Ēthrane (enflurane) with epinephrine used for hemostasis is such that up to 10 ml of 1:100,000 or 1:200,000 epinephrine solution may be injected subcutaneously over a 10 minute period. Up to 30 ml of epinephrine solution may be administered over the period of an hour.
- **Minimal or no liver changes**
  Ēthrane (enflurane) has produced either no change or small, transient increases in liver enzymes. Repeated enflurane anesthesias also have not significantly altered these values[2–6].
- **Minute-by-minute control**
  With a blood/gas partition coefficient of only 1.9, Ēthrane (enflurane) provides for a rapid induction and for rapid changes in depth to meet varying needs of surgery and patient management.
- **Potentiation of nondepolarizing relaxants**
  Clinical use suggests that ½ to ⅓ the usual dose of nondepolarizing relaxant is required when anesthesia is obtained with enflurane[7]. This potentiating effect helps reduce the risk of residual or recurring postanesthetic paralysis.
- **Rapid recovery; minimal anesthetic after-effect**
  Because of enflurane's low solubility in blood, patients emerge from anesthesia promptly with little or no depression of mental function or residual symptomatic effect.

1. Dobkin AB, Nishioka K, Gengaje DB, et al: Ethrane (compound 347) anesthesia: a clinical and laboratory review of 700 cases. Anesth Analg 48:477-493, 1969.
2. Botty C, Brown B, Stanley V, et al: Clinical experiences with compound 347, a halogenated anesthetic agent. Anesth Analg 47:499-505, 1968.
3. Lebowitz MH, Blitt CD, Dillon JB: Clinical investigation of compound 347 (Ethrane). Anesth Analg 49:1-10, 1970.
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5. Virtue RW, Lund LO, Phelps JR, et al: Difluormethyl 1,1,2-trifluoro-2-chloroethyl ether as an anesthetic agent: results with dogs and a preliminary note on observations with man. Canad Anaesth Soc J 13:233-241, 1966.
6. Allen PJ, Downing JW: A prospective study of hepatocellular function after repeated exposure to halothane or enflurane in women undergoing radium therapy for cervical cancer. Brit J. Anaesth 49:1035-1039, 1977.
7. Hanquet M: Enflurane (Ethrane) anesthesia. A survey of the first 1000 cases. Acta Anaesthesiol Belg 25:289-299, 1974.

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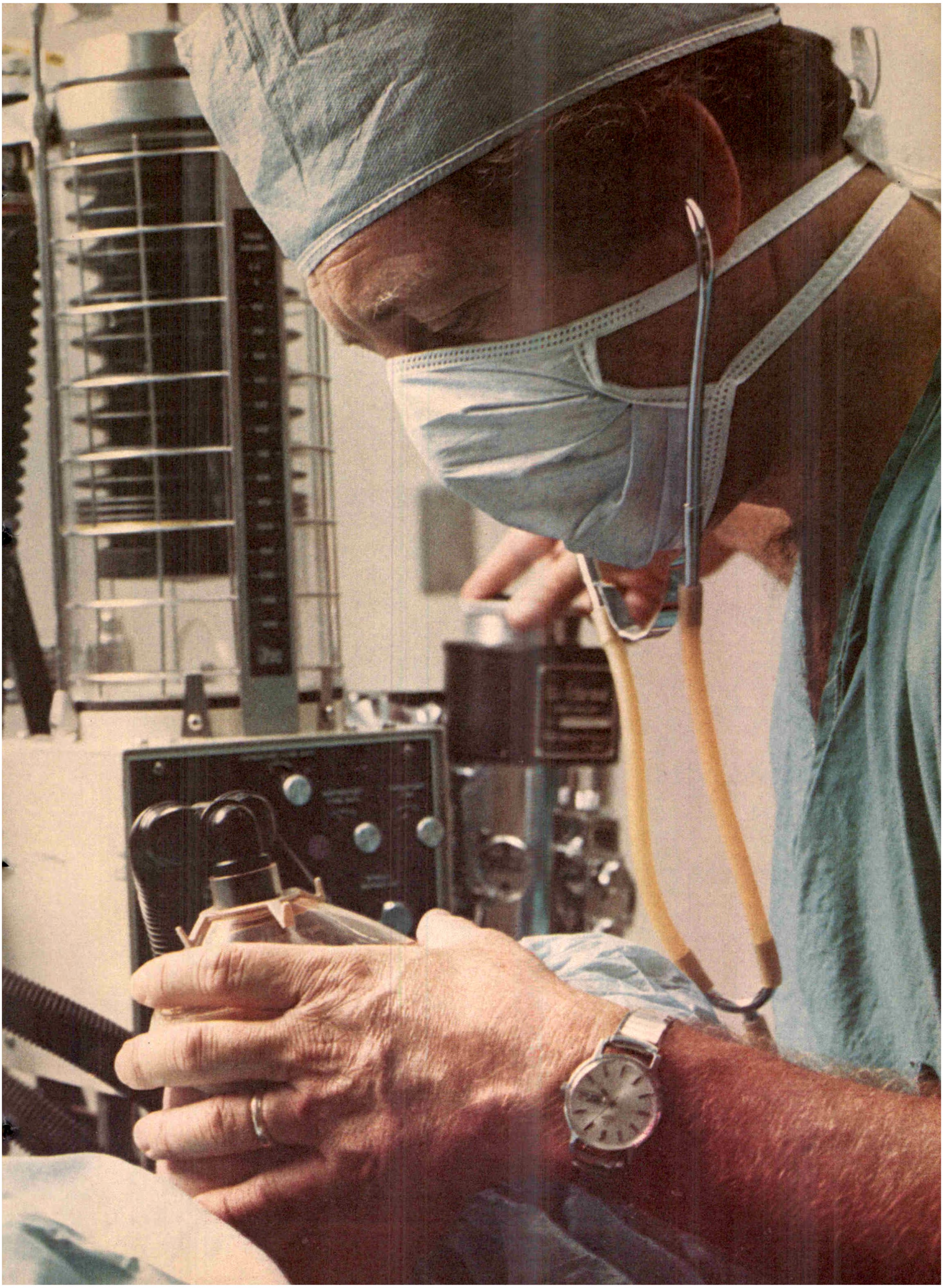
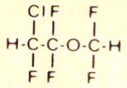


Ēthrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ĒTHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



$$\mathrm{H{-}\overset{\displaystyle Cl}{\underset{\displaystyle F}{C}}{-}\overset{\displaystyle F}{\underset{\displaystyle F}{C}}{-}O{-}\overset{\displaystyle F}{\underset{\displaystyle F}{C}}{-}H}$$

The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \quad A = 7.967$$
$$B = -1678.4$$
$$T = {}^\circ C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ĒTHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ĒTHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ĒTHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

ACTIONS

ĒTHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ĒTHRANE are rapid. ĒTHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ĒTHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ĒTHRANE. ĒTHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ĒTHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ĒTHRANE anesthesia. ĒTHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ĒTHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ĒTHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ĒTHRANE.

Biotransformation of ĒTHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ĒTHRANE anesthesia in man in the absence of surgery. Thus ĒTHRANE does not depress this aspect of the immune response.

INDICATIONS

ĒTHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ĒTHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ĒTHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ĒTHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ĒTHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ĒTHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ĒTHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ĒTHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ĒTHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ĒTHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ĒTHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ĒTHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ĒTHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ĒTHRANE mixture. In general, inspired concentrations of 3.5-4.5% ĒTHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ĒTHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ĒTHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

PACKAGING

ĒTHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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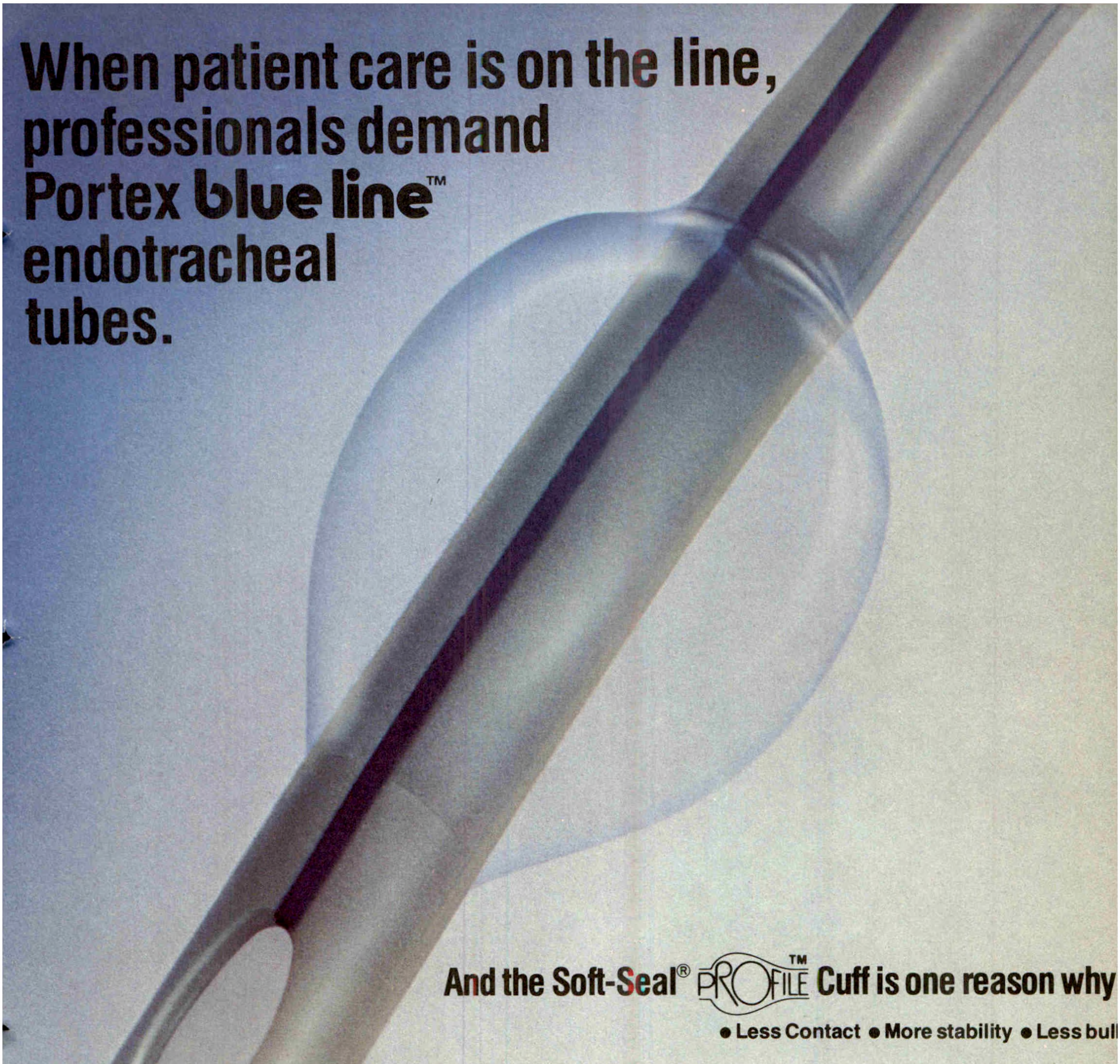

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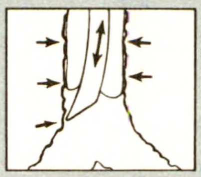

- Larger area of old shape has much more contact with trachea wall, thus more potential for tracheal wall irritation.
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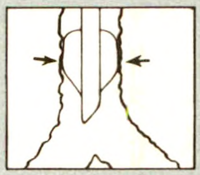

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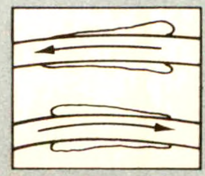

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NEUTRALIZES THE NEGATIVE

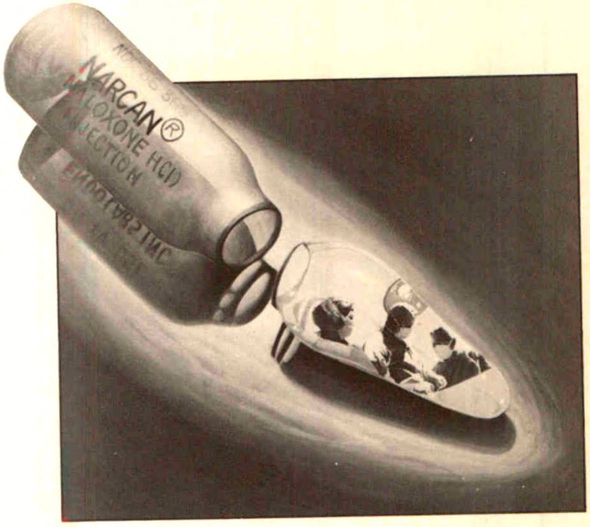
NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

Useful when narcotic/N_2O anesthesia is employed

Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism



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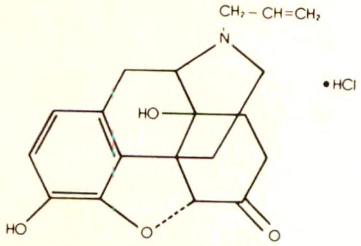
naloxone HCl

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



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(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

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NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN® (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

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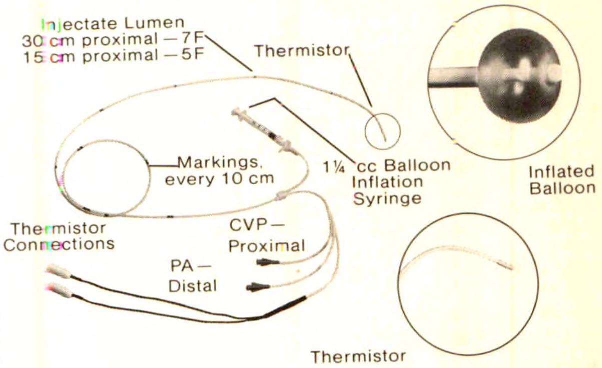

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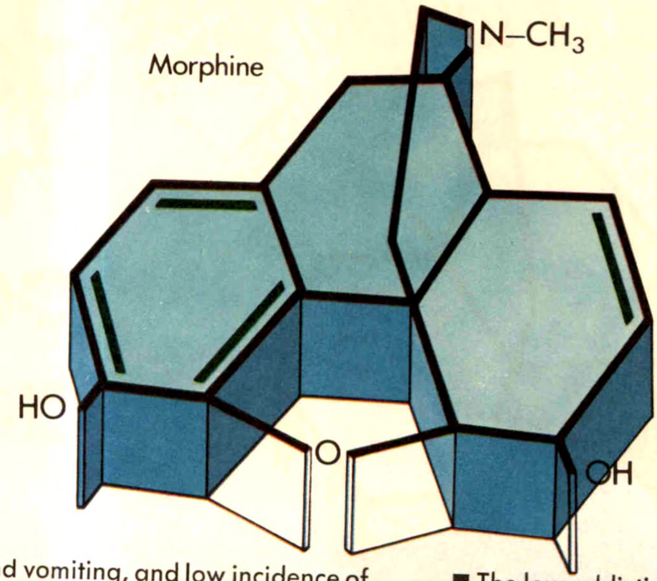


Important option when potent parenteral analgesics are indicated

■ Standard doses of Stadol are as effective in relieving pain as standard doses of both morphine[1-4] and meperidine.[5-7, 37]

■ By either I.M. or I.V. route—provides prompt onset of analgesia, achieves peak activity rapidly, maintains effects for 3–4 hours.

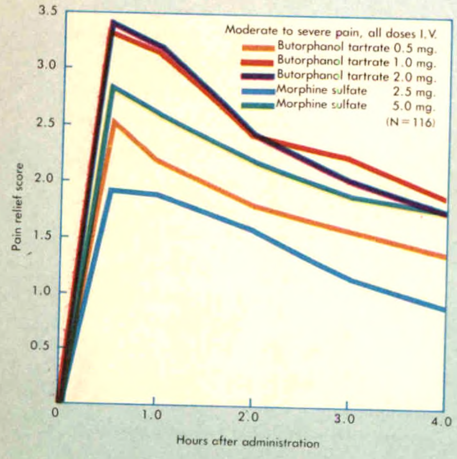
■ Distinguished by its favorable side effects profile,[1-16, 31-33, 36, 37]—low physical-dependence liability, limited respiratory depressant effect, little nausea and vomiting, and low incidence of CNS effects other than sedation.

■ 2 mg. of Stadol produces an order of respiratory depression similar to that caused by 10 mg. of morphine. In contrast to morphine, increasing Stadol doses yield greater analgesic effect,[9] without appreciably increasing liability for respiratory depression.[16]

■ The low addictive potential of Stadol[24] is underscored by its narcotic antagonist properties.

Stadol is not recommended for patients physically dependent on narcotics or with significant previous narcotic experience. Its use in such patients, without prior detoxification, will result in induction of withdrawal reactions.

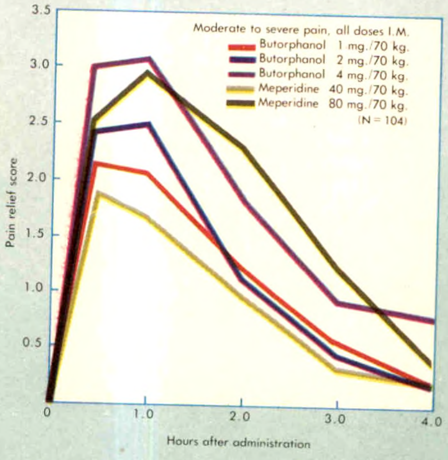
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate and morphine sulfate

In this study "... butorphanol tartrate 0.5 mg produced greater relief than morphine sulfate 2.5 mg and butorphanol tartrate 1.0 and 2.0 mg produced greater relief than morphine sulfate 5.0 mg." **(DelPizzo[1])**

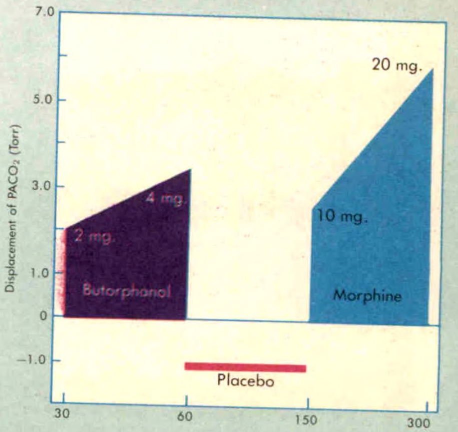
Unsurpassed pain relief



Average mean pain relief scores
In response to butorphanol tartrate and meperidine hydrochloride

In moderate to severe pain, butorphanol tartrate provided relief "... that was not statistically distinguishable from that achieved with 80 mg/70 kg meperidine." **(Gilbert et al[5])**

Limited respiratory depressant effect

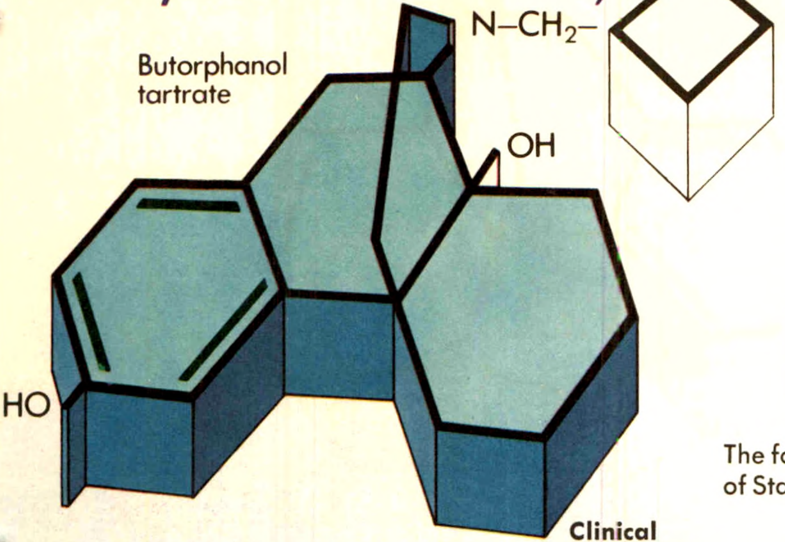


Log dose PACO2 displacement curves

In this graph based on alveolar carbon dioxide tension ($PACO_2$) measurements, the flatter the curve, the less respiratory depression. "The flat dose-response curve ... of butorphanol may indicate that, because of its antagonistic properties, there is a limit to its respiratory depressant effects. **(Adapted from Nagashima et al[16])** **Unlike morphine with its steep dose-response curve, the magnitude of respiratory depression does not increase in a dose-related manner with Stadol, within the range of recommended doses.**

Stadol® IM IV

(butorphanol tartrate)



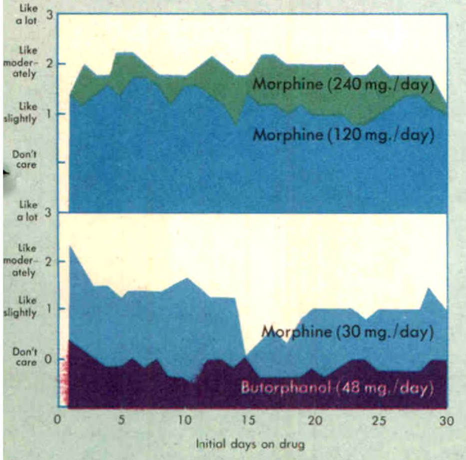
closer to the ideal parenteral analgesic

The following table shows a side-by-side clinical comparison of Stadol with both morphine and meperidine.

Clinical parameters	Meperidine	Morphine	Stadol
Control status	Schedule II	Schedule II	**Nonscheduled**
Indication	moderate to severe pain	moderate to severe pain	**moderate to severe pain**
Standard I.M. dose	75–100 mg.	8–10 mg.	**2 mg. (1 to 4 mg.)**
Standard I.V. dose	50–100 mg.	4–10 mg.	**1 mg. (0.5 to 2 mg.)**
Usual route of administration	I.M./I.V.	I.M./I.V.	**I.M./I.V.**
Onset of pain relief	30 minutes I.M., very rapidly I.V.	30 minutes I.M., very rapidly I.V.	**less than 30 minutes I.M., very rapidly I.V.**
Peak analgesic activity	within 1 hour I.M., within 30 minutes I.V.	within 1 hour I.M., within 20 minutes I.V.	**within 1 hour I.M., within 30 minutes I.V.**
Duration of pain relief I.M./I.V.	slightly less than morphine	about 4 hours	**3–4 hours**
Addicting potential	high	high	**low**
Respiratory effects	dose-related depression	dose-related depression	**limited depression—no appreciable dose-related increase within the range of recommended doses.**

Data for this table were obtained from: Jaffe, J. H. and Martin, W. R.: Narcotic analgesics and antagonists, in The Pharmacological Basis of Therapeutics (Goodman, L. S. and Gilman, A., eds.), ed. 5, New York, Macmillan, 1975, pp. 245–283; AMA Drug Evaluations, ed. 3, Chicago, 1977, pp. 325–339; and from manufacturer recommendations.

Low physical-dependence liability



Preference scores completed by subjects during chronic butorphanol tartrate administration compared with scores from three other groups of subjects receiving 30, 120 and 240 mg. of morphine daily. (Adapted from Jasinski et al[24])

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In moderate to severe pain...

Stadol® IM IV

(butorphanol tartrate)

INDICATIONS AND USAGE— (1) 8/18/78

Stadol is recommended for the relief of moderate to severe pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients physically dependent on narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical-dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head injury and increased intracranial pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular effects: Because Stadol increases the work of the heart, especially the pulmonary circuit (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain respiratory conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired renal or hepatic function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage in pregnancy: The safety of Stadol for use in pregnancy has not been established; therefore, this drug should be used in pregnant patients only when, in the judgment of the physician, its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in labor and delivery: Safety to the mother and fetus following administration of Stadol during labor and delivery has not been established.

Usage in nursing mothers: The use of Stadol is not recommended in nursing mothers since it is not known whether this drug is excreted in human milk.

Pediatric use: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

CNS effects: nervousness, unusual dreams, agitation, euphoria, hallucinations

Autonomic effects: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: vomiting

Respiratory: slowing of respiration, shallow breathing

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors, and assisted or controlled respiration.

DOSAGE AND ADMINISTRATION—*Adults:* Intramuscular—The usual recommended single dose is 2 mg. This may be repeated every three to four hours, as necessary. The effective dosage range, depending on the severity of pain, is 1 to 4 mg. repeated every three to four hours. At this time, there is insufficient clinical data to recommend single doses beyond 4 mg.

Intravenous—The usual recommended single dose for intravenous administration is 1 mg. repeated every three to four hours as necessary. The effective dosage range, depending on the severity of pain, is 0.5 to 2 mg. repeated every three to four hours.

Children: Since there is no clinical experience in children under 18 years, Stadol is not recommended in this age group.

Storage conditions: When stored at room temperature, the stability of the solution in vials is 2 years.

SUPPLY—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, 2 mg. per ml., 2-ml. vial; 1 mg. per ml., 1-ml. vial; 2 mg. per ml., 1-ml. vial; 2 mg. per ml., 10-ml. multi-dose vial.

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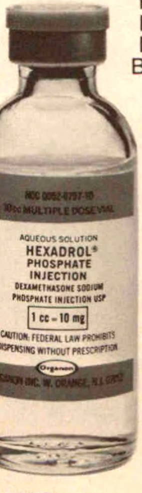
ACTIONS—Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune response to diverse stimuli.

CONTRAINDICATIONS—Systemic fungal infections—Hypersensitivity to any component.

WARNINGS—In patients on corticosteriod therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated. Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage In Pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.



100 mg

Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Patients with stressed myocardium should be observed carefully and the drug administered slowly since premature ventricular contractions may occur with rapid administration. Dietary

All corticosteroids increase calcium excretion.

WHILE ON CORTICOSTEROID THERAPY PATIENTS SHOULD NOT BE VACCINATED AGAINST SMALLPOX. OTHER IMMUNIZATION PROCEDURES SHOULD NOT BE UNDERTAKEN IN PATIENTS WHO ARE ON CORTICOSTEROIDS, ESPECIALLY IN HIGH DOSES BECAUSE OF POSSIBLE HAZARDS OF NEUROLOGICAL COMPLICATIONS AND LACK OF ANTIBODY RESPONSE.

The use of Hexadrol Phosphate Injection (dexamethasone sodium phosphate injection, USP) in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculosis regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.

PRECAUTIONS—Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocu-

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction must be gradual.

Psychic derangements may appear when corticosteroids are used ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection, also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully followed.

Intra-articular injection of a corticosteroid may produce systemic as well as local effects.

Appropriate examination of any joint fluid present is necessary to exclude a septic process.

A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and the diagnosis of sepsis is confirmed, approrpriate antimicrobial therapy should be instituted.

Local injection of a steroid into a previously infected joint is to be avoided. Corticosteroids should not be injected into unstable joints.

ADVERSE REACTIONS—

Fluid and electrolyte disturbances: Sodium retention; Fluid retention; Congestive heart failure in susceptible patients; Potassium loss; Hypokalemic alkalosis; Hypertension.

Musculoskeletal: Muscle weakness; Steroid myopathy; Loss of muscle mass; Osteoporosis; Vertebral compression fractures; Aseptic necrosis of femoral and humeral heads; Pathologic fracture of long bones.

Gastrointestinal: Peptic ulcer with possible subsequent perforation and hemorrhage; Pancreatis; Abdominal distention; Ulcerative esophagitis.

Dermatologic: Impaired wound healing; Thin fragile skin; Petechiae and ecchymoses; Facial erythema; Increased sweating; May suppress reactions to skin tests.

Neurological: Convulsions; Increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; Vertigo; Headache.

state; Suppression of growth in children; Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, sugery, or illness; Decreased carbohydrate tolerance; Manifestations of latent diabetes mellitus; Increased requirements for insulin or oral hypoglycemic agents in diabetics.

Ophthalmic: Posterior subcapsular cataracts; Increased intraocular pressure; Glaucoma; Exophthalmos.

Metabolic: Negative nitrogen balance due to protein catabolism.

Miscellaneous: Hyperpigmentation or hypopigmentation; Subcutaneous and cutaneous atrophy; Sterile abscess; Postinjection flare, following intra-articular use; Charcot-like arthropathy; Itching, burning, tingling in the ano-genital region.

DOSAGE AND ADMINISTRATION—For treatment of unresponsive shock high pharmacologic doses of this product are currently recommended. Reported regimens range from 1 to 6 mg/kg of body weight as a single intravenous injection to 40 mg initially followed by repeat intravenous injection every 2 to 6 hours while shock persists.

DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENTS.

CAUTION—Federal law prohibits dispensing without prescription.

HOW SUPPLIED—5-cc (4 mg/cc) multiple dose vial, NDC #0052-0796-05; 1-cc (4mg/cc) vial, box of 25, NDC #0052-0796-25; 10-cc (10mg/cc) vial (for intravenous or intramuscular use only), NDC #00520-0797-10;
1-cc (4mg/cc) Prefilled Disposable Syringe (for intravenous or intramuscular use only) NDC #0052-0796-26.

Hexadrol is available in two potencies, 4mg/cc and 10mg/cc in aqueous solution with 1% benzyl alcohol as preservative.

When You Need it... Hexadrol Has It!

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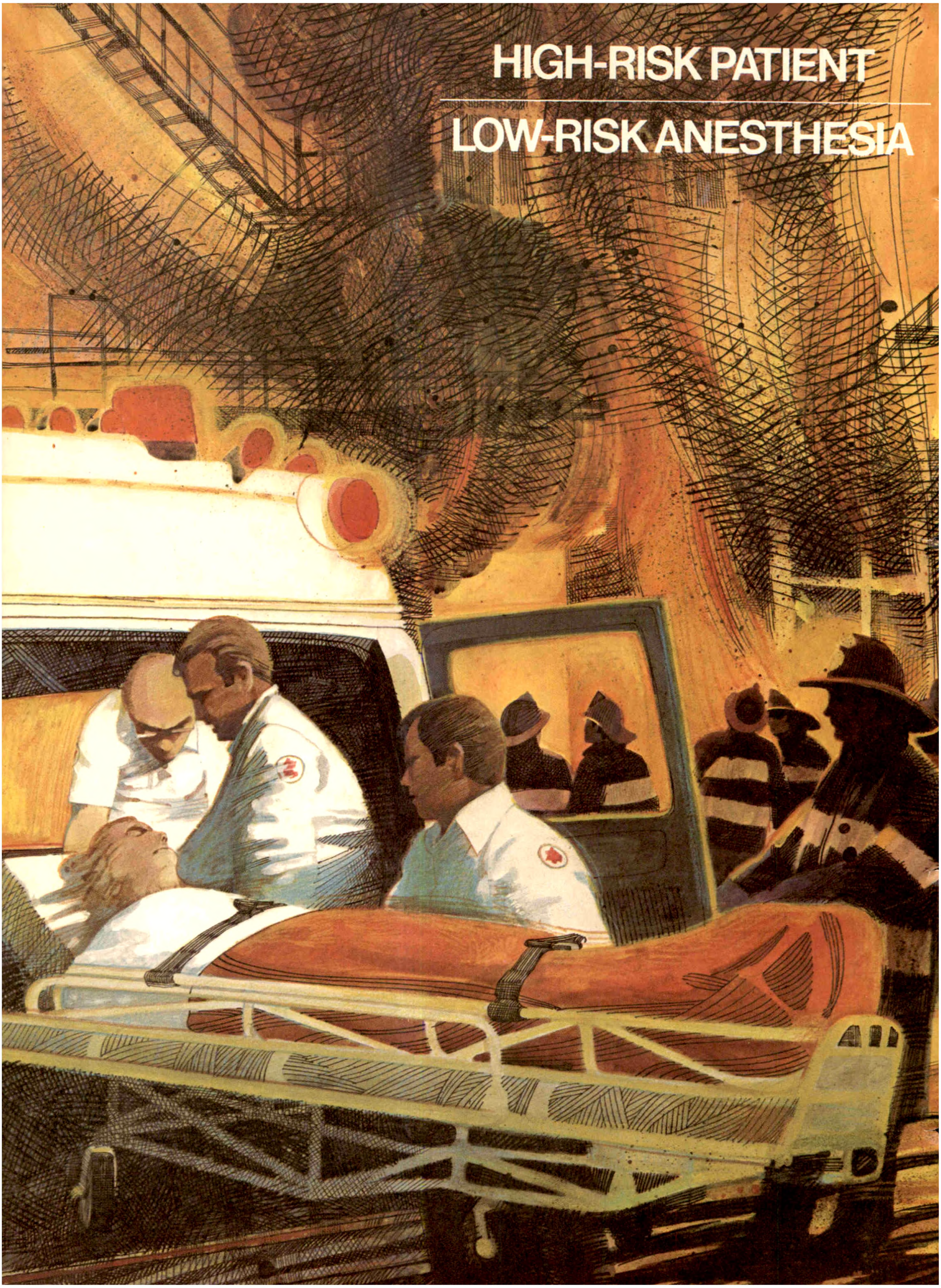
HIGH-RISK PATIENT
LOW-RISK ANESTHESIA

Ketalar®

(ketamine hydrochloride injection, NF)

Features you need...

Smooth, rapid onset of anesthesia, profound analgesia, IM or IV administration. Little risk of liver damage or buildup of tolerance following repeated procedures. Ketalar usually strengthens, rather than depresses, blood pressure, pulse rate and respiration. When necessary, it permits maintenance of unaided respiration because of minimal relaxation of skeletal muscles or laryngeal-pharyngeal reflexes.

for the patients who need them

At either end of the age spectrum, the pediatric or geriatric patient. The patient in shock, or with shock potential. Patients in whom establishing an IV route of administration is difficult. The burn patient requiring repeated dressing changes. Patients requiring manipulative or diagnostic procedures. The debilitated patient. The emergency patient who may not have an empty stomach.

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA-SHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemcially incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy: Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. **The incidence of emergence reactions may be reduced** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with pre-anesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15 – Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4581-12 – Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4582-10 – Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.
N 0071-4585-08 – Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.

SG

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Division of Warner-Lambert Company
Morris Plains, NJ 07950

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Now, an anticholinergic for use in anesthesia with significant advantages over atropine...

Robinul® Injectable

(Glycopyrrolate Injection, NF)

- Little or no CNS effect
- Prolonged vagal blocking effect
- Longer antisialagogue activity

See last page for

PRE-OPERATIVELY

- Protects against excessive pharyngeal and bronchial secretions.
- Protects against excessive volume and acidity of gastric secretions—a danger if pulmonary aspiration occurs.
- Protects against vagal reflexes at time of intubation.

INTRA- OR POST-OPERATIVELY

- Protects against arrhythmias and bradycardia associated with drugs used for reversal of muscle relaxants (e.g. neostigmine).
- Protects against surgically-induced vagal reflexes.

Robinul® Injectable (Glycopyrrolate Injection, NF)

an anticholinergic with significant advantages over atropine

Situation	**Objective**	**Action**
preoperative	Reduction of gastric secretions plus elevation of gastric pH above 2.5 to help protect against serious sequelae of aspiration.	Use Robinul Injectable in the premedication regimen.
induction of anesthesia	To have unobstructed view of glottis prior to tracheal intubation. To help protect against vagal reflexes during intubation.	Use Robinul Injectable in the premedication regimen.
intra-operative	To help protect against surgically or drug induced vagal reflexes.	Use Robinul Injectable intraoperatively.
post-operative	To help prevent excess peripheral muscarinic effects of cholinergic agents used in the reversal regimen.	Use Robinul Injectable in the reversal regimen.
recovery room	To help prevent "central anticholinergic syndrome."	Use Robinul Injectable whenever an anticholinergic is used.

Each 1 ml contains:
Glycopyrrolate, NF .... 0.2 mg
Water for Injection, USP .... q.s.
Chlorobutanol, USP (preservative) 0.5%

For intramuscular or intravenous administration in conjunction with anesthesia.

Contraindications: There are no absolute contraindications to the use of Robinul Injectable in conjunction with anesthesia except known hypersensitivity to glycopyrrolate.

Warnings: This drug should be used with great caution, if at all, in patients with glaucoma or asthma.

Precautions: ***Usage in Pregnancy.*** The use of any drug in pregnancy, lactation, or in the childbearing age requires that the potential benefits of the drug be weighed against the possible hazards to mother and child. Reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate. However, diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

Use with caution in patients with: myasthenia gravis; coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertension.

The intravenous administration of any anticholinergic in the presence of cyclopropane anesthesia can result in ventricular arrhythmias; therefore, caution should be observed if Robinul (glycopyrrolate) Injectable must be used during cyclopropane anesthesia. If the drug is given in small incremental doses of 0.1 mg or less, the likelihood of producing ventricular arrhythmias is reduced.

Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur.

Adverse Reactions: Anticholinergics produce certain effects most of which are extensions of their fundamental pharmacological actions. Adverse reactions to anticholinergics in general may include dry mouth; urinary hesitancy and retention; blurred vision due to mydriasis; increased ocular tension; tachycardia; palpitation; decreased sweating; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestation; some degree of mental confusion and/or excitement, especially in elderly persons.

Dosage and Administration: Robinul (glycopyrrolate) Injectable may be administered intramuscularly, or intravenously, without dilution, in the following indications:

Adults: ***Preanesthetic Medication.*** The recommended dose of Robinul (glycopyrrolate) Injectable is 0.002 mg (0.01 ml) per pound of body weight by intramuscular injection, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Robinul (glycopyrrolate) Injectable may be used during surgery to counteract drug-induced or vagal traction reflexes with the associated arrhythmias (e.g., bradycardia). It should be administered intravenously as single doses of 0.1 mg (0.5 ml) and repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Children: ***Preanesthetic Medication.*** The recommended dose of Robinul (glycopyrrolate) Injectable in children up to 12 years of age is 0.002 mg to 0.004 mg (0.01 ml to 0.02 ml) per pound of body weight intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Because of the long duration of action of Robinul (glycopyrrolate) if used as preanesthetic medication, additional Robinul (glycopyrrolate) Injectable for anticholinergic effect intraoperatively is rarely needed; in the event it is required the recommended pediatric dose is 0.002 mg (0.01 ml) per pound of body weight intravenously, not to exceed 0.1 mg (0.5 ml) in a single dose which may be repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended pediatric dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Compatibility With Other Agents: ***Known compatibilities.*** Robinul (glycopyrrolate) Injectable is compatible for mixing and injection with the following: 5% and 10% glucose in water or saline; Demerol® (meperidine) Injectable; morphine sulfate; Innovar® (fentanyl plus droperidol) Injectable; Vistaril® (hydroxyzine) Injectable; Prostigmin® (neostigmine) Injectable; Mestinon® (pyridostigmine) Injectable. Robinul Injectable may be administered via the tubing of a running infusion of physiological saline or lactated Ringer's solution.

Known incompatibilities include the following injectables: sodium bicarbonate; Valium® (diazepam); sodium pentobarbital; various phenothiazines; Dramamine® (dimenhydrinate), and chloramphenicol.

Drug Interaction During Anesthesia. Glycopyrrolate has been used clinically with at least the following medications: a barbiturate (sodium thiopental); narcotic analgesics (morphine, alphaprodine hydrochloride, fentanyl); sedative/tranquilizers (droperidol, diazepam); gaseous anesthetics (nitrous oxide); volatile liquid anesthetics (diethyl ether, halothane, methoxyflurane, enflurane); parenteral anesthetics (ketamine); peripherally-acting skeletal muscle relaxants (succinylcholine, gallamine, d-tubocurarine, pancuronium); cholinergic agents (neostigmine, pyridostigmine); and other anticholinergics (atropine).

There are no known unique or unanticipated drug-drug interactions with other agents except that Robinul (glycopyrrolate) Injectable should be used with caution if at all during cyclopropane anesthesia (see Precautions).

Management of Overdosage: To combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulfate may be given in a dose of 1.0 mg for each 1.0 mg of Robinul (glycopyrrolate) Injectable known to have been administered.

How Supplied: Robinul (glycopyrrolate) Injectable is available in 1 ml single dose vials; and 5 ml and 20 ml multiple dose vials (NDC 0031-7890). Rev. Aug. 1976

A.H.Robins Company, Richmond, Va. 23220

A·H·ROBINS

for intramuscular or intravenous administration in conjunction with anesthesia

Robinul® Injectable

(Glycopyrrolate Injection, NF)

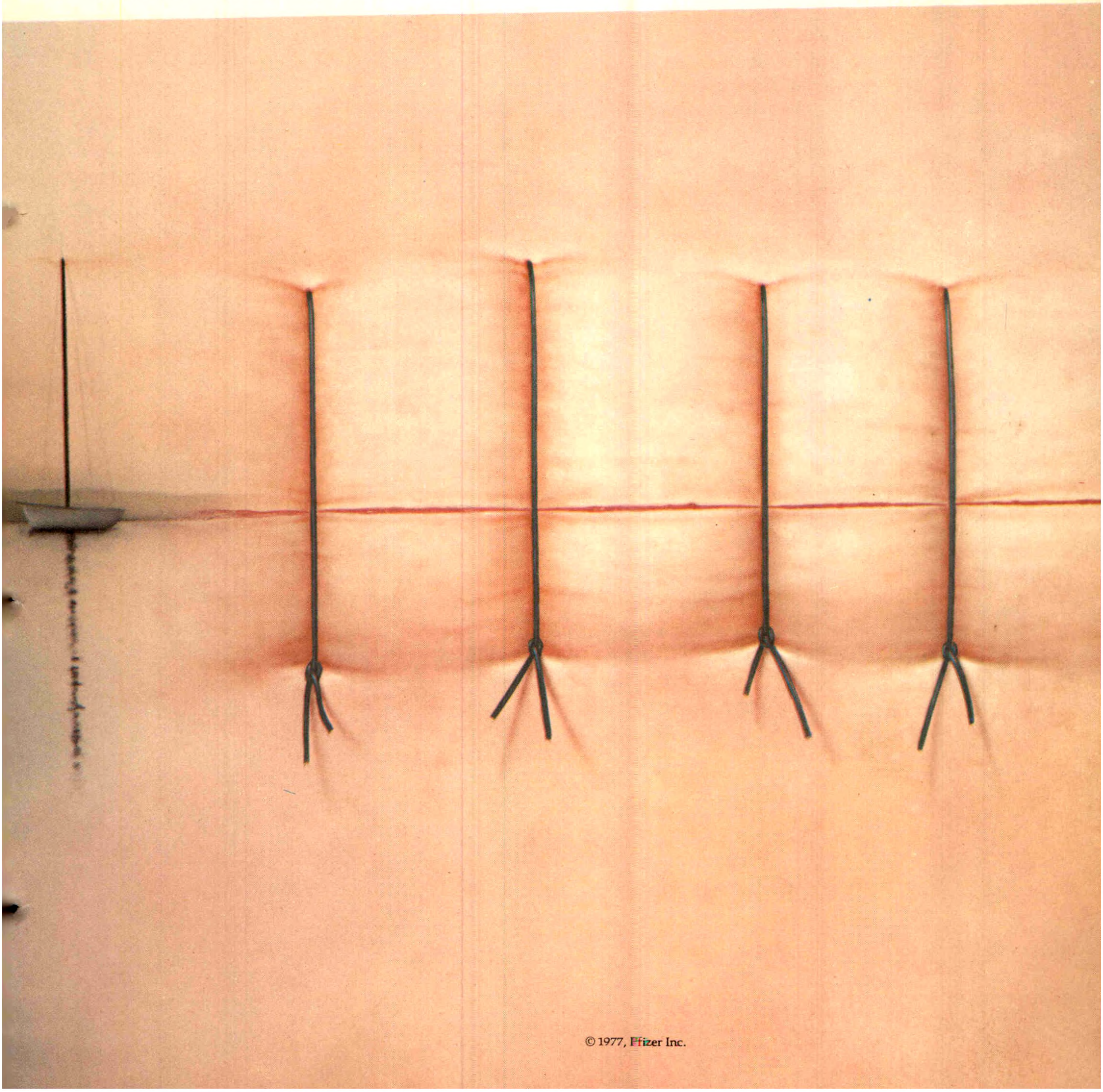
The Calm introduction to surgery

Vistaril® I.M.

(hydroxyzine HCl)

—allays anxiety
—reduces narcotic requirements
—and controls emesis

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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Vistaril® I.M.

(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

**preoperatively
and
postoperatively**

- **allays presurgical anxiety... allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY

VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml–10 ml vials; 50 mg/ml–2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml–1 ml fill; 100 mg/2 ml–2 ml fill.

Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)

VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)

More detailed professional information available on request.

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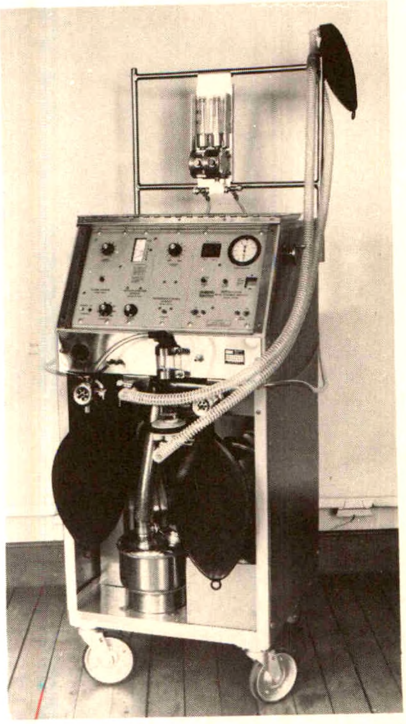

Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

Please request Form 3-MV.

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54th CONGRESS to be held MARCH 9-13, 1980

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MEETING INFORMATION

PRE-REGISTRATION MATERIAL, HOTEL CARD, PROGRAM

This information will be mailed in December to all I.A.R.S. members, associate members, and educational members.

(Individuals outside of U.S. who plan to attend, please advise I.A.R.S. Cleveland office by December 1st to assure timely arrival of pre-registration material.

SCIENTIFIC EXHIBIT SPACE

Requests for applications for scientific exhibit space should be sent to: B. B. Sankey, M.D., International Anesthesia Research Society, Cleveland, Ohio 44122. Please note that scientific exhibit applications can be accepted—on a space availability basis—up to January 15, 1980.

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EDITORIAL

How May Neuromuscular Blocking Drugs Affect the State of General Anesthesia?

MANY of us have probably noted the following development during abdominal surgery under light general anesthesia supplemented with muscle relaxants: The patient suddenly, and unexpectedly, becomes "tight" and at the same time seems too lightly anesthetized. Are these two circumstances simply coincidental, or are they related in any way? The traditionalists among us might explain the matter just as inadequate maintenance of anesthesia. Certainly, few clinicians would blame the apparent lightening of the patient's state of consciousness on inadequate maintenance of dosage of a neuromuscular blocking drug. The paper by Forbes, Cohen, and Eger[1] in this issue of *Anesthesia and Analgesia*, however, does suggest that at least one neuromuscular blocker (pancuronium) may supplement the anesthetic state (MAC).

In this study, 17 halothane-anesthetized patients received pancuronium (0.1 mg/kg) while 18 did not. Pancuronium was excluded from three extremities by pneumatic tourniquets, and was injected intravenously into one arm. MAC was determined in standard fashion by observation of movement of the isolated extremities in response to surgical incision. Pancuronium was found to lower halothane MAC from 0.73% to 0.55%. This appears to be a well-documented demonstration in man of an interaction between the general anesthetics and the neuromuscular blockers on sensory pathways, whether or not the sensory routes in question are affected peripherally or centrally.

Until the past decade, classic peripheral cholinergic pharmacology involved the interaction of acetylcholine and its inhibitors (including neuromuscular blocking agents) at nicotinic receptors (neuromuscular junction and autonomic ganglia), at muscarinic receptors at postganglionic parasympathetic neuroeffector junctions, and at esteratic receptors (on the active sites of the enzymes acetylcholinesterase and the nonspecific plasma cholinesterase). The subject, however, has become more complicated. Now, additional nicotinic and muscarinic cholinergic receptors modulating *catecholamine* release at peripheral *adrenergic* nerve terminals are well-known.[2] Furthermore, two *different* types of cholinergic receptors are now postulated to be involved with transmission in sympathetic ganglia, one (the so-called M_e receptor) promoting slow depolarization of ganglion cells (a *facilitatory* pathway) and one (the M_i receptor) subserving transmission within an *inhibitory* pathway.[3] Both pancuronium and gallamine are now known to produce their side effects (tachycardia and increased blood pressure) by not only inhibiting muscarinic receptors in the sinus node of the heart[4,5] (the "vagolytic" effect), but also by inhibiting the M_i receptors[3] and the muscarinic receptors on adrenergic neuron terminals described above.[3,6] The latter actions in effect "facilitate" sympathetic nervous system activity and increase catecholamine release. The preceding remarks highlight only a few of many new facets of the currently broadening pharmacology of neuromuscular blockers, including pancuronium.

Note especially that all of pancuronium's effects in the peripheral autonomic nervous system involve blockade of muscarinic receptors. It is true that the neuromuscular junction is classified as a *nicotinic* site, and that, indeed, pancuronium is a potent neuromuscular blocker; but its effects at other nicotinic sites (such as ganglia) are minimal.[5] It is, therefore, not a classic nicotinic blocker like *d*-tubocurarine. In contrast, the latter drug, and its derivative, metocurine, produce their autonomic effects by blockade of nicotinic receptors (the ganglion-blocking action).[7] They have very little effect on muscarinic receptors. Nondepolarizing neuromuscular blockers, therefore, fall into two classes according to their preponderance of either nicotinic or muscarinic side effects in the peripheral autonomic nervous system. In fact, the cholinergic receptors at the neuromuscular junction should probably not be labeled "nicotinic," but should receive separate classification. What about the central nervous system (CNS)?

Certainly many cholinergic pathways, subserving a variety of behavioral functions such as memory and learning, temperature control, appetite, aggression, and, especially pertinent to this discussion, sleep, have been described within the brain.[8, 9] Both nicotinic and muscarinic pathways probably do exist.[10] Therefore, neuromuscular blocking drugs might affect some of these circuits provided that they could enter the CNS in great enough concentration. Pancuronium, since it has been shown to inhibit muscarinic receptors at several sites within the peripheral autonomic nervous system, might presumably act on this type receptor within the CNS.

Matteo's work[11, 12] certainly shows that relatively low concentrations of *d*-tubocurarine can be detected within the spinal fluid of man after ordinary clinical doses given intravenously. Although not yet demonstrated, the same might be true for pancuronium. Therefore, we might assume that enough pancuronium might reach cholinergic receptors in the brain to exert a measurable influence on certain behavioral patterns subserved by cholinergic pathways, including sleep. Sleep, of course, is not anesthesia; and general anesthetics have a global influence on the brain, do not act specifically on any receptor type, and, therefore, do not preferentially affect any cerebral function, although some evidence does suggest that one important action of general anesthetics may be an inhibition of the ascending reticular formation, an area responsible for maintenance of wakefulness.[13, 14] However, agents promoting sleep, such as thiopental and diazepam, are commonly used to supplement general anesthetics.

If pancuronium blocks muscarinic receptors in the CNS, then, in order to lower MAC as suggested by Forbes et al[1] it might act on muscarinic receptors in the ascending reticular activating system, which involves cholinergic pathways.[14-18] This system, when activated, produces an arousal response mimicked by cholinergic antagonists and by anticholinesterases.[18] Inhibition of this pathway by a specific antagonist (pancuronium?) might lead to supplementation of a sleep-influence and in turn a lowering of MAC.

The foregoing discussion is admittedly grossly oversimplified. There are many cholinergic pathways within the brain, and probably many different cholinergic receptor types modulating transmission along a variety of other routes (e.g., adrenergic, gabaminergic, etc.). It is difficult to imagine that a muscarinic antagonist such as pancuronium might lower MAC by an action on only one pathway. Rather, the end-result probably represents a complex algebraic sum of inhibitory effects of pancuronium on many muscarinic receptors in a large number of cerebral circuits. The observation that a neuromuscular blocking drug which blocks muscarinic receptors may augment general anesthesia is novel but does seem plausible and, of course, needs further substantiation. The novelty of the subject raises several questions. For example, will other neuromuscular blockers have the same effect on MAC as pancuronium? Gallamine, another muscarinic inhibitor, might indeed have a similar effect; but the nicotinic blockers, *d*-tubocurarine and metocurine, and the nicotinic and muscarinic stimulant, succinylcholine, might interact in an entirely different fashion. If pancuronium lowers MAC, why do neuromuscular blockers, when injected directly intraventricularly, cause convulsions? Do the observations of Forbes et al[1] have any clinical significance? Answers to these questions may not be apparent for several years, but it is possible that an improved knowledge of the CNS effects of neuromuscular blockers may lead to a better understanding of the state of general anesthesia and to an improvement of our clinical practice.

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Preoperative Pulmonary Preparation

A group of 157 patients with chronic obstructive pulmonary disease who were treated before surgery, using a standardized pulmonary preparation, underwent physiologic assessment both before and after the prophylactic program. The postoperative course of each patient also was evaluated to assess the incidence of respiratory morbidity and mortality. Although many physiologic values were statistically improved after the pulmonary preparation, most of the changes are of doubtful functional significance. It is difficult to determine which patients will develop pulmonary complications not requiring mechanical ventilation. However, the group requiring this type of support appears to be predictable on the basis of the severity of their pulmonary functional impairment and their lack of response to the standard pulmonary preparation used. The single most reliable test for this purpose was the mean forced expiratory flow during the middle half of the forced vital capacity. The frequency of postoperative respiratory complications was related to the type of operation, with the highest incidence occurring in the group that had extensive surgery of the upper abdomen. While the occurrence of these complications was significantly reduced in patients undergoing a standard preoperative pulmonary preparation, the explanation for the beneficial effect of this procedure is not apparent. *(Gracey DR, Divertie MB, Didier EP: Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease: a prospective study. Chest 76:123–129, 1979)*

ANESTH ANALG
58:452–456, 1979

Ethanol, Diazepam, and Scopolamine Alter Murine Learning Function and Memory; Ethanol Changes Halothane Minimum Alveolar Concentration

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AMIRDIVANI, M., CHALON, J., RAMANATHAN, S., AND TURNDORF, H.: Ethanol, diazepam, and scopolamine alter murine learning function and memory; ethanol changes halothane minimum alveolar concentration. Anesth Analg 58:452–456, 1979.

The minimum alveolar anesthetic concentration of halothane (MAC_h) was tested by the tail clamping method in 12 male white albino mice and found to be 1.1%. A further 24 mice were given 15% alcohol to drink for 60 days, after which they were divided into four groups of six mice each. One group was tested for MAC_h immediately after withdrawal from alcohol and the remaining groups were tested 4, 10, and 18 days later. In the first group MAC_h was 0.6%. It rose to 1.1% 4 days later and gradually reached 1.6% after an additional 14 days. Before receiving alcohol the mice were starved for 24 hours and placed in a maze containing food. The time taken to reach the food was recorded. The mice completed their way through the maze in 147 ± 21 seconds on the first run and in 73 ± 10 seconds on a second run, after which they made no further significant progress. During the first 9 days on alcohol mice made their way through the maze in an average of 178 ± 17 seconds (no memory). On the 10th day they went through the maze in 160 ± 17 seconds on the first run (still no memory) but in 59 ± 8 seconds on a second run (regained learning function) ($p < 0.0005$). A control group of six mice trained in the maze continued to cover it at maximal speed after a rest period of 10 days. An additional seven mice were given diazepam, 0.33 μg/g of body weight and another six mice, scopolamine, 0.13 μg/g of body weight, both intraperitoneally. They had been previously trained in the maze. Both groups lost their memory and ability to learn their way through the maze but regained the latter in a week. Alcohol, diazepam, and scopolamine all induce retrograde amnesia and loss of learning function, but the latter returns after 8 to 10 days. It is difficult to correlate the loss of memory and the ability to learn caused by alcohol with the changes alcohol produces in MAC_h.

Key Words: ALCOHOL: memory and learning; ALCOHOL: inhalation anesthetic potency; HYPNOTICS, Benzodiazepines: diazepam; PREMEDICATION: scopolamine; PREMEDICATION: diazepam.

PREVIOUS STUDIES have shown that acute alcoholic intoxication decreases halothane MAC (MAC_h) whereas chronic alcoholism increases it both in animals and man.[1-5] Others have studied the amnesic effects of diazepam and scopolamine in man and animals.[6-9] They have shown that diazepam produced temporary nonretrograde loss of memory in man,[6-8] and amnesia in mice but only if the animals were in the learning stage.[9]

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We have studied the possible relationships between memory and ability to learn in mice at various stages of alcoholism and compared our findings with changes in MAC_h when alcohol was withdrawn. We also examined the effects of diazepam and scopolamine on murine memory and ability to learn. and we have observed similarities between the effects of these drugs and that of alcohol. Our experiments were conducted under controlled conditions to confirm or disprove previous studies and to provide information which may have been missed by other workers.

Methods

Fifty-eight normal male albino mice, weighing between 28 and 32 g each, were subjects for the study. Three died during intraperitoneal injections. Three sets of experiments were conducted on the remaining 55 mice (Fig 1).

Experiment 1 (Controls)

Eighteen mice served as controls for the experiments described below. Six mice (Controls A) were trained to find their way through a maze containing food‖ (Fig 2) after 24 hours of starvation. The mean time taken to reach the food was noted for each of six trials. Maze tests were repeated after a rest period of 10 days. These standards were strictly adhered to in all experiments conducted thereafter. No less than six tests were performed in each instance.

The remaining 12 mice were used to assess MAC_h using the tail clamping method.[10] The mice were restrained supine by taping their limbs, tail, and maxilla to a dissection board and securing the tape with pins. The anterior aspect of the neck was shaved and the trachea was exposed under local anesthesia with 0.2 ml of 0.125% bupivacaine. A 20-gauge Teflon catheter 1.5 cm in length was inserted into the trachea to a depth of 1 cm and ligated in situ. A miniature 3-way stopcock, dead space 0.1 ml, with a tuberculin syringe at its free end, was inserted between the catheter connector and a T-piece anesthesia circuit. The chest was inflated at a rate of 80/mm[11] by intermittently occluding the free end of the circuit with a finger, using a fresh gas inflow of 0.5% to 3% halothane in O_2 at a rate of 2 L/min. Gas samples (0.5 ml) were aspirated from the trachea into the syringe by switching the 3-way stopcock. Halothane concentrations were assessed by introducing the first 0.4 ml in the syringe into an ultraviolet analyzer. Minimal alveolar concentration was estimated both during induction of anesthesia and after the anesthesia had been discontinued; the average of both values was considered MAC_h.

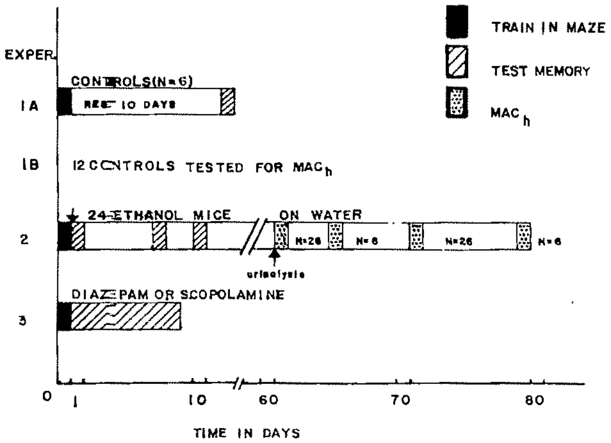

Fig 1. Time sheet of experiments performed.

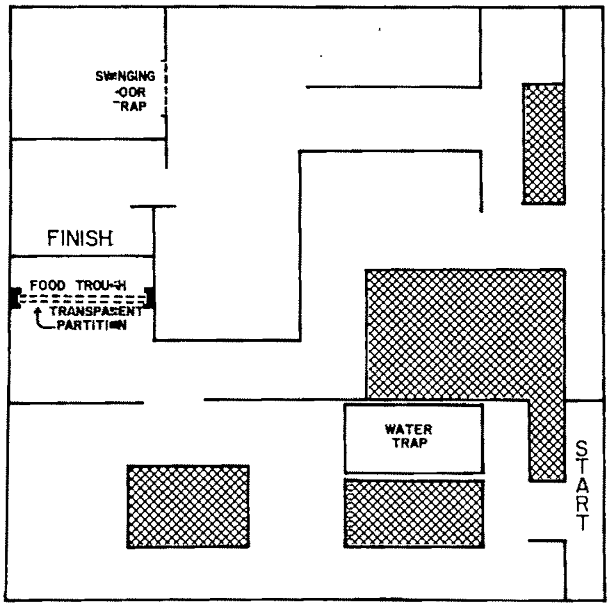

Fig 2. Maze used to test the learning ability and memory of mice. The swinging trap door was hinged at the top. Mice could enter the trap but took about 30 seconds to get out. They only got trapped on their first run when intoxicated or drugged. Habituation to alcohol prevented recurrence of this event. The hatched areas are impenetrable.

Experiment 2 (Alcohol)

A group of 24 mice was starved for a day and trained to find their way through the maze. Statistically significant improvements in time to reach the food were noted. Their water supply was then replaced by 15% ethanol, weight for weight in water, for 2 months. During their early period on ethanol they were retested in the maze (days 1, 7, and 10). When the 2 months were over, urine alcohol concentration was tested enzymatically by alcohol dehydrogenase. The mice were then divided into four equal groups and MAC_h was determined in the first group immediately after the mice were removed from their cages. The other three groups were given water to drink instead of alcohol, and MAC_h was determined 4, 10, and 18 days later.

‖ All animals ate Lab-Blox, 8604-00 (Allied Mills, Inc, Chicago, Illinois), because they were weaned from mothers which were fed the same diet.

Experiment 3 (Diazepam and Scopolamine)

A group of 13 mice were taught to find their way through the maze, after which seven of them received diazepam, 0.33 μg/g of body weight and six received scopolamine hydrobromide, 0.13 μg/g of body weight (both administered intraperitoneally). They were retested daily in the maze for 8 days.

Results were expressed as a mean measurement for each group studied (±1 SE). Statistical significance was assessed by commonly used variance techniques (chi-square, t-test); $p < 0.05$ was considered statistically significant.

Results

The average daily consumption of alcoholic solution was between 2 and 3 ml per mouse. This included spillage and evaporation. Urine alcohol on the morning of the 60th day averaged 29 ± 2 mg/100 ml.

Experiment 1 (Controls)

The group A mice learned to find their way through the maze in one run. They initially took 147 ± 10 seconds to reach the food (Fig 3) and 65 ± 14 seconds on the second run ($p < 0.005$). The third run was performed in 58 ± 8 seconds which was not statistically faster than the second run. The mice remembered the maze after a rest period of 10 days. MAC_h of the 12 control B mice was 1.1%.

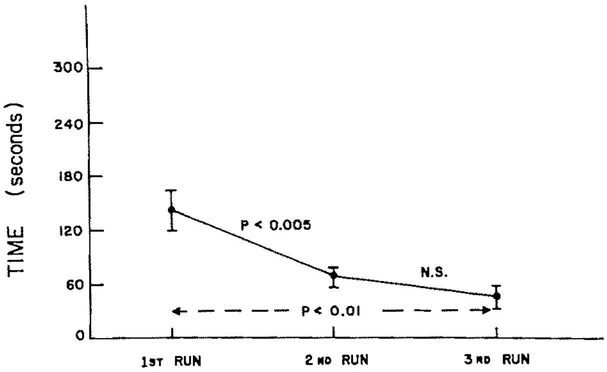

FIG 3. Speeds at which control mice found their way through the maze. The second run (73 ± 21 seconds) was significantly faster than the first run (147 ± 21 seconds, $p < 0.005$). The third run (59 ± 22 seconds) was not significantly more rapid than the second.

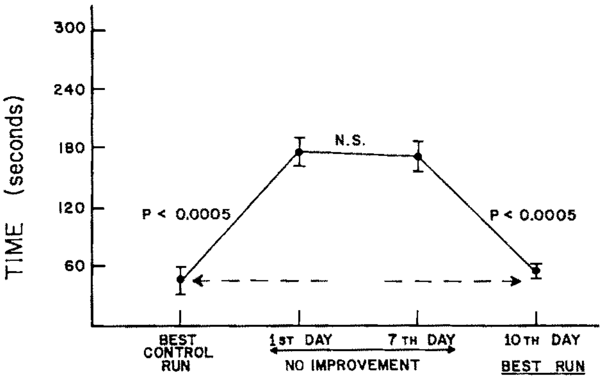

FIG 4. Nonalcoholic control mice (left) were able to find their way through the maze in 59 ± 22 seconds. Alcoholic mice (center) who had learned the maze could neither recall nor relearn their way through the maze (days 1 and 7 compared to best controls), but regained their ability to learn although not their memory by day 10 (second run 59 ± 8 seconds compared to 160 ± 28 seconds during first run as noted in text).

Experiment 2 (Alcohol)

Before drinking alcohol the 24 mice covered the maze in 147 ± 21 seconds on their first run and in 73 ± 10 seconds on their second run ($p < 0.0005$), after which they made no further significant progress (58 ± 15 seconds). After 1 day on alcohol and up to day 7, the mice lost their ability to remember the maze and to improve on successive runs. Mean time to reach the food (Fig 4) was 178 ± 17 seconds on day 1 and 180 ± 16 seconds on day 7 ($p < 0.0005$ compared to second control run, and to second run before drinking alcohol). By day 10 they regained their ability to learn but not their memory. They first completed their way through the maze in 160 ± 28 seconds, and in 59 ± 8 seconds on their second run. MAC_h was 0.6% immediately after removal from alcohol (Fig 5) and then gradually rose, reaching 1.6% 18 days later.

Experiment 3 (Diazepam and Scopolamine)

The mice went through the maze in 90 ± 16 seconds on their second run before treatment with diazepam. After receiving the drug they took 235 ± 42 seconds ($p < 0.0025$) and failed to improve on several runs during the next 7 days. On the 8th day they still failed to remember the maze (152 ± 48 seconds on their

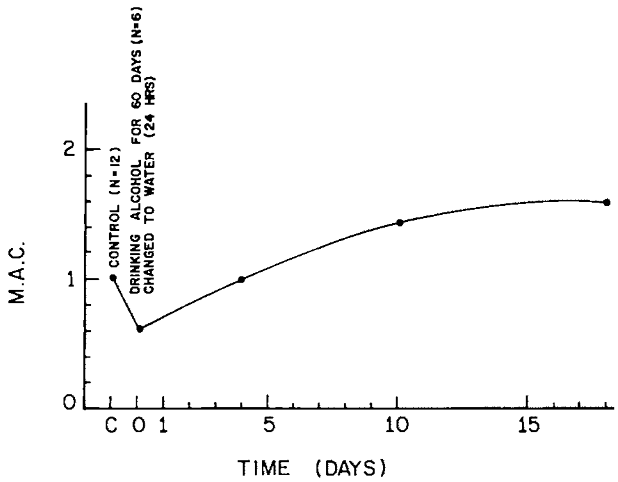

FIG 5. Effects of alcohol on MAC$_h$. At the end of 60 days of drinking alcohol, MAC$_h$ averaged 0.6 ± 0.05% ($p < 0.0005$ compared to control MAC$_h$ values averaging 1.0 ± 0.05%). Four days after withdrawal from alcohol, MAC$_h$ averaged 1.0 ± 0.06 (not significantly different from controls). After 18 days of withdrawal from alcohol, MAC$_h$ averaged 1.6 ± 0.04% ($p < 0.005$ compared to controls).

first run) but regained their learning power, covering the maze in 58 ± 15 seconds on their second run ($p < 0.05$). Mice that were to receive scopolamine reached the food in the maze in 76 ± 5 seconds in their second run, but took 200 ± 41 seconds the day after injection ($p < 0.0125$). The mice took approximately the same time to complete the maze during the next 7 days but by the 8th day they had regained their learning ability but not their memory (first run 132 ± 34 seconds and second run 81 ± 15 seconds, $p < 0.05$).

Discussion

The return of learning ability in our chronically alcoholic mice after 10 days (Fig 4) was probably due in part to cerebral neuronal habituation to alcohol and in part to hepatic microsomal enzyme induction by ethanol,[2, 3, 5] in particular induction of alcohol dehydrogenase, the enzyme which accelerates metabolism of ethanol into acetaldehyde, acetic acid, and finally CO_2 and H_2O.

It is not possible to ascribe the increase in MAC$_h$ after withdrawal from alcohol (Fig 5) to increased metabolism of halothane due to microsomal enzyme induction produced by ethanol; several workers have shown that the rate of metabolism of inhalation anesthetics does not affect MAC.[12-14] Immediately after chronic alcoholic intoxication MAC$_h$ was, however, significantly decreased, presumably because of the combined action of ethanol and halothane on the brain. As blood levels of alcohol and the products of its metabolism were eliminated there was a gradual increase in MAC$_h$ to well above control levels. This was presumably due to changes in the central nervous system brought about by the continuous use of ethanol. Chronic exposure to alcohol results in reduction in neuronal excitability threshold, phospholipid demyelination, and an increase in phospholipid content of the white matter.[1]

Mice that were to receive diazepam required longer than control mice to find their way through the maze on the second run even before diazepam was given. After the drug was injected they took even longer to run through the maze than any other group. This is probably a reflection of variations in intelligence between different groups of animals. However, since each group acted as its own control, these variations did not affect the significance of the observed effects of diazepam on the memory and the ability to learn.

One injection of diazepam produced retrograde amnesia and interfered with learning ability for 8 days in our series, contrary to the findings of Bohdanecky and Jarvik[9] and Frumin et al.[6] Scopolamine produced findings similar to those produced by diazepam. Our results differ from those of Bohdanecky and Jarvik[9] who found that mice receiving scopolamine became amnesic only during the learning stage. Their experimental design was simpler than ours and included only four alternatives, whereas our maze incorporated 13 possible detours, a trap, and a water barrier (total 15). The difference between our results and those of Frumin et al,[6] who found nonretrograde amnesia after preanesthetic treatment with diazepam and scopolamine, is presumably due to the dosages that we used and which are above those used in clinical practice. For instance 0.33 µg of diazepam per gram for a 30-g mouse amounts to a total of 9.9 µg. A 70-kg man given the same dose in micrograms per gram would receive 23.1 mg, which is well above the clinical dose of 5 to 10 mg. Similar calculations would produce a 9-mg dose of scopolamine for the same man, who would normally receive 0.4 to 0.6 mg as pre-anesthetic medication. The results of our studies in mice of the effects of diazepam and scopolamine on memory and the ability to learn cannot, therefore, be directly applied to man. However, our results suggest that the effects of these two drugs on cerebral cortical function be further evaluated in man.

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Dexamethasone Use in Head Injury

A prospective double-blind study of the effects of dexamethasone administration on the outcome of patients with severe head injuries was performed. Patients were treated with placebo, low-dose dexamethasone (16 mg/day), or high-dose dexamethasone (96 mg/day) for a period of 6 days. Outcome was evaluated at 6 months following injury. Of the 76 patients available for analysis, a good outcome was achieved in 37% of placebo-treated patients, 44% of low-dose-treated patients, and 29% of high-dose-treated patients. These differences are not statistically significant. Similarly dexamethasone administration had no statistically significant effect on intracranial pressure patterns or serial neurologic examinations during hospitalization. Good outcome was associated with age under 10 years, lighter depth of coma on admission, and the preservation of brain stem reflexes upon admission. A recalculation of data in previous clinical series purporting to show an improvement in outcome as a result of corticosteroid therapy shows no significant difference in outcome when steroid- and placebo-treated patients are compared. In this series 90% of all deaths were caused by recurrent intracranial hematomas, medical complications, or diffuse brain injuries with parenchymal hemorrhage and tissue disruption; causes of death that cannot be affected by corticosteroid therapy. The study suggests that dexamethasone in either high or low dosages has no significant effect on morbidity and mortality following severe head injury. *(Cooper PR, Moody S, Clark WK, et al: Dexamethasone and severe head injury: a prospective double-blind study. J. Neurosurg 51:307-316, 1979)*

ANESTH ANALG
58:457-460, 1979

Limitations of the Cyanide Electrode for Use in Plasma and Whole Blood

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KISTNER, J. R., LONGNECKER, D. E., MILLER, E. D., JR., AND LESCANIC, A. D.: Limitations of the cyanide electrode for use in plasma and whole blood. Anesth Analg 58:457–460, 1979.

Although the cyanide ion-specific electrode has been used for the measurement of cyanide in biologic fluids, its validity has not been documented under these conditions. Therefore, we analyzed 60 paired samples of blood and plasma in a blinded fashion and compared the cyanide ion concentrations obtained from the ion-specific electrode with those obtained from a standard chemical assay. There was poor correlation between results in plasma samples ($r = .52$, $n = 26$) and no correlation in whole blood ($r = .02$, $n = 34$). Until refinements of the electrode technique are made, this method cannot be recommended for the measurement of cyanide in biologic fluids.

Key Words: PHARMACOLOGY: nitroprusside; TOXICITY: cyanide; MEASUREMENT TECHNIQUES: cyanide.

THE POTENTIAL for serious cyanide toxicity resulting from the infusion of large quantities of sodium nitroprusside is widely recognized.[1,2] The clinical signs of toxicity including acidosis, increased lactate levels, and increased venous P_{O_2} are useful but occur only when tissue respiration has already been compromised.[2] A rapid and reliable means of measuring cyanide in blood or plasma might be valuable in recognizing potential cyanide toxicity. Unfortunately, current methods for measuring cyanide take 1 to 2 hours to perform and therefore provide little help in an acute situation.

The availability of an ion-specific electrode (Orion Research cyanide ion electrode model 94-06) designed for industrial cyanide determinations seems to offer an advantage in speed and simplicity and has resulted in the use of this technique for cyanide measurement in biologic samples, either blood or plasma. Although several investigators have reported results using this electrode,[3,4] neither the validity nor sensitivity of this technique has been documented in biologic fluids. This study was designed to compare the results obtained with the ion-specific electrode technique to those obtained from a standard chemical assay for cyanide.[5]

Materials and Methods

Appropriate functioning and response of the electrode in nonbiologic fluids was evaluated by the addition of potassium cyanide (KCN) to distilled water. Calibration curves for cyanide in the biologic fluids were constructed in the following manner: 5-ml samples of whole blood or plasma were diluted to 20 ml with distilled water after alkalinization with 200 μl of 10 M NaOH. Known amounts of KCN were then incrementally added. With the electrode directly in the biologic fluid, the resultant changes in electrode potential (millivolts) were digitally displayed (Orion 70/A digital PH/MV meter) and recorded.

The electrode uses a solid membrane containing inorganic silver compounds. When the membrane is in contact with a cyanide solution, silver ions dissolve from the membrane surface and are replaced by other silver ions from within the membrane, setting up a potential electrical difference related to the cyanide ion concentration.

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The chemical assay that we used was the Rodkey and Collison[5] modification of Boxer and Rickards'[6] method of cyanide determination. Two major steps are involved. First, cyanide is separated from thiocyanate by acidifying blood or plasma causing the release of cyanide as HCN. The HCN is subsequently trapped in a small quantity of distilled water rendered alkaline by sodium hydroxide. Second, the amount of cyanide present in the alkaline fluid is determined by converting the cyanide to the cyanogen chloride which is reacted with a pyridine/pyrazolone mixture. The color is measured with a spectrophotometer (629 nm) and the absorbance obtained is proportional to the quantity of cyanide present.[7]

Information regarding the validity, sensitivity, and reproducibility of this chemical method are readily available in the literature.[5-7] In our laboratory the recovery rate for known quantities of KCN added to plasma is >95%. The assay is sensitive to cyanide concentrations less than 0.2 μM. Within day measurements are reproducible to ±1.5%, day to day measurements to ±3%. As a further check of validity, samples containing known amounts of cyanide were assayed by this method in a blinded fashion. When the results of the assay were compared to the known quantities of cyanide added, the actual and measured values had a correlation of .99.

Blood and plasma from three different sources were used to test the validity of the electrode measurements. First, using 22-day-old bank blood, "unknown" samples were prepared by the addition of known amounts of KCN to plasma (N = 8) and blood (N = 16). The change in millivolts of electrode output was converted to estimated cyanide concentration using a calibration curve constructed by incremental addition of KCN to a sample from the same unit of blood.

In a second experiment, increasing amounts of nitroprusside were infused in a dog. A total of 36 paired samples of plasma and whole blood were analyzed in a blinded fashion by both the standard chemical assay and the ion-specific electrode. Electrode calibration curves were constructed by the incremental addition of KCN to a preinfusion sample of the dog's blood. Saline infusion and vasopressor support were administered so that enough nitroprusside could be administered to cause death from cyanide toxicity. Clinical signs of cyanide toxicity, including metabolic acidosis and marked elevation of mixed venous P_{O_2} (obtained from a Swan-Ganz catheter), were present.

Last, paired blood samples (N = 12) from patients receiving nitroprusside were analyzed in a blinded fashion by the chemical and electrode techniques. Again, calibration curves were constructed using a preinfusion blood sample from each patient.

Results

The ion-specific electrode functioned in distilled water according to specifications. A typical calibration curve is shown in Fig 1. The slope of this curve approximated 60 mV/log change in cyanide ion concentration [CN⁻] between 10^{-5} and 10^{-3} M. The slope became slightly erratic from 10^{-5} to 10^{-6} M and progressively more flat from 10^{-6} to 10^{-7} M inscribing a curve very similar to that expected by the manufacturer.[‖] Lower limits of sensitivity appeared to be about 0.5 μM. Fig 1 also depicts a typical calibration curve obtained by the incremental addition of KCN to plasma or whole blood. The electrode is less sensitive with the slope of the curve approximating 30 mV/log change in [CN⁻].

Fig 2 depicts the [CN⁻] determined with the electrode vs either the known [CN⁻] (1st group) or the [CN⁻] determined by the standard chemical method (2nd or 3rd groups). The correlation coefficient for the pooled results in plasma is r = .52 (N = 26); for whole blood r = .02 (N = 34).

Discussion

Because of the widespread use of sodium nitroprusside, the potential for cyanide toxicity, and the difficulty in the diagnosis of cyanide toxicity before signs of tissue anoxia, a simple and rapid method for measurement of blood and plasma [CN⁻] would be desirable. While the relative simplicity of the cyanide electrode is appealing, it does not appear to have sufficient sensitivity or reliability when used directly in biologic fluids. Even when measuring [CN⁻] in distilled water, the useful lower limit of sensitivity appeared to be about 0.5 μM. A commonly used approach for analysis includes the dilution of a 5-ml blood or plasma sample to 20 ml with distilled water (J. E. Cottrell and P. Casthely, personal communication). The [CN⁻] of a sample thus diluted would need to be 2 μM to distinguish it from background. Since patients receiving therapeutic amounts of nitroprusside usually have a plasma [CN⁻] level of <2 μM and a level of 4 μM may be associated with early signs of cyanide toxicity,[1] the electrode seems to lack sufficient sensitivity even if it could be made to function reliably in biologic fluids.

[‖] Orion Cyanide Ion Specific Electrode information booklet.

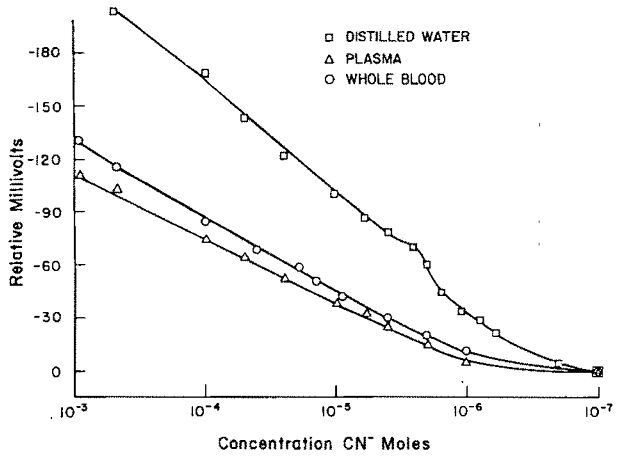

FIG 1. Typical calibration curves obtained by the incremental addition of KCN to distilled water, plasma, and whole blood.

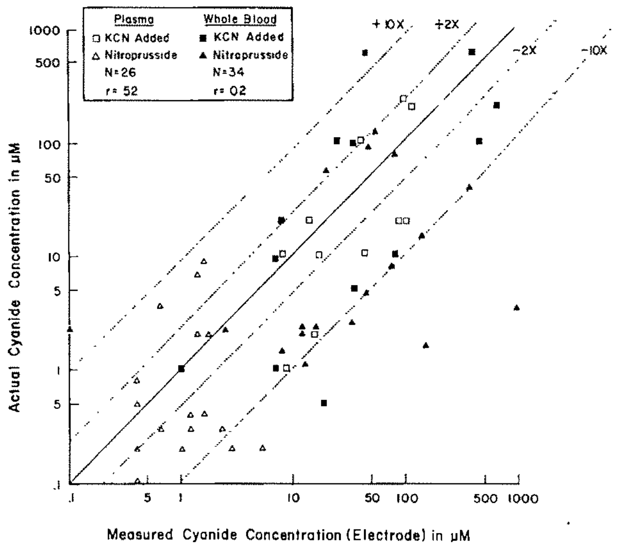

FIG 2. CN levels measured using an electrode are plotted against the known (by weight) CN levels or chemically determined CN values. Since the log-log scale makes the correlation appear better than it actually is, the dotted lines parallel to the line of identity are included to define 2-fold and 10-fold error limits.

The lower limit of electrode response is determined by the slight water solubility of the membrane. In samples with low [CN⁻], the electrode responds to cyanide ions dissolved from the membrane, as well as cyanide ions in the sample. Therefore linearity of response is impaired when measuring [CN⁻] <10 μM.||

More important than the lack of sensitivity, however, is the lack of validity. Although the correlation coefficient between the two methods in plasma is statistically significant ($r = .52$, $N = 26$, $p = 0.01$) this is a poor correlation for two laboratory tests which presumably measure the same substance. Further the [CN⁻] values in whole blood lack even statistical correlation. Of great concern was the fact that occasionally the electrode measured extremely high values of whole blood [CN⁻] in patients in whom there were no clinical signs of toxicity. The chemical method found substantially lower values.

The possible hypothesis that the ion-specific electrode values were correct while the chemical results were not is contradicted by several points: (1) the first group of blood samples had a known cyanide ion concentration; (2) the chemical method has undergone scrutiny in terms of recovery rates, sensitivity, and comparison to other means of cyanide determination; (3) the blood [CN⁻] as determined by Rodkey's method correlated well with progressive signs of tissue anoxia in the dog (beginning about 30 μM) whereas the values determined with the electrode showed no such tendency.

We can only speculate on why the electrode fails to function properly in biologic fluids. Progressive baseline drift was observed which may have been caused by deposition of proteinaceous material on the electrode. This problem is also seen with other electrode techniques in biologic fluids. When cellophane with 40- to 60-A pores, designed to permit access to cyanide ions but prevent protein buildup, was applied over the electrode, the baseline drift was partially but not completely corrected.

It is likely that the electrode can be used for cyanide measurement[9] if one first removes the cyanide from the biologic fluid (M. Tark, personal communication). This can be accomplished either using nitrogen as a carrier gas[5] or with a microdiffusion chamber.[9] In either case the biologic fluid is acidified, releasing HCN, which is recaptured in an alkaline solution. The ion-specific electrode is then employed to measure [CN⁻] in the alkaline solution. Used in this manner, with the necessary preliminary separation, the electrode loses its advantages of speed and simplicity and still lacks the sensitivity of the colorimetric reaction.[7]

We conclude that the direct measurement of cyanide in plasma and whole blood by a specific ion electrode technique does not give valid results when compared to an established chemical assay for cyanide. Unless further refinements permit documentation of validity, sensitivity, and reproductivity, this method is unacceptable for the measurement of [CN⁻] in biologic fluids.

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Cardiovascular Effects of Positive-Pressure Ventilation

In normal subjects during 15 minutes of positive-pressure ventilation with 10 cm H_2O end-expiratory pressure (PEEP), cardiac output fell 19%, due to a fall in stroke volume. Transmural mean right atrial pressure rose 3.1 cm H_2O and right ventricular end-diastolic diameter increased 15%. Simultaneously, left ventricular end-diastolic diameter decreased 21%, ejection time increased 11%, and velocity of circumferential fiber shortening fell 30%. Thus, right ventricular filling increased and left ventricular filling decreased. The function of the right ventricle was impaired and the function of the left ventricle may have been impaired. Cardiac output gradually increased due to a 7% increase in heart rate as PEEP was continued for 1 hour and transmural mean right atrial pressure also increased further by 2.4 cm H_2O. Compensation for the reduced stroke volume occurred as filling pressures and heart rate rose, but ventricular function remained impaired for the entire duration of PEEP. On resumption of spontaneous breathing, cardiac output and ventricular function returned to baseline levels. The authors conclude that the reduced cardiac output during PEEP is not due to a direct mechanical reduction in right ventricular filling. *(Cassidy SS, Eschenbacher WL, Robertson CH Jr, et al: Cardiovascular effects of positive-pressure ventilation in normal subjects. J Appl Physiol 47: 453–461, 1979)*

ANESTH ANALG
58:461-465, 1979

The Celiac Ganglia in Man: Normal Anatomic Variations

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WARD, E. M., RORIE, D. K., NAUSS, L. A., AND BAHN, R.C.: The celiac ganglia in man: normal anatomic variations. Anesth Analg 58:461-465, 1979.

The celiac ganglia and plexus were examined during autopsy in 20 adult bodies. The size of the ganglia and their relationships to the celiac artery were determined by direct measurement; their relationships to the anterior vertebral column and to different vertebral levels were determined by roentgenography after markers outlining the ganglia had been applied. The celiac ganglia were found to vary in diameter from 0.5 to 4.5 cm, in number from 1 to 5, and in location from the middle of the second lumbar vertebra to the intervertebral disk between the T-12 and L-1 vertebrae. The average distances of the ganglia below the celiac artery on the right and left sides were 0.6 and 0.9 cm, respectively. Most frequently, the ganglia were less than 1.5 cm in front of the anterior vertebral margin, as determined by lateral roentgenographic views. These findings indicate that celiac plexus block is most likely to be successful if the needle on the left side is placed so that the tip is at the level of the junction of the middle and lower thirds of the first lumbar vertebra and if the needle on the right side is placed approximately 1 cm higher. The needle tips should be placed from 1 to 1.5 cm anterior to the anterior vertebral margin. Use of computed tomography for locating the celiac artery and ganglia before blocks gave inconsistent results.

Key Words: ANATOMY: celiac plexus; ANESTHETIC TECHNIQUES, Regional: celiac plexus.

PAIN from advanced, unresectable carcinoma of the pancreas or stomach is difficult to manage. Pain relief from narcotics often is either not possible or accompanied by undesirable side effects. One method used to control pain associated with these malignancies is block of the celiac plexus. Success rates in relieving abdominal and back pain with the block are difficult to evaluate because pain relief is subjective, but reported rates vary from 33%[1] to 94%.[2] Even with success rates of 94%, however, the results were excellent in only 60% of patients, and 14 of 34 blocks were classified as good only after they had been repeated. An extensive study done by de Takats[3] of 1712 cases abstracted from the literature showed a 75% success rate. Possible reasons for the generally high rate of unsuccessful block include lack of diffusion of the drug through the retroperitoneal space, injection of too little drug, addiction of the patient to narcotics, improper placement of needles, and anatomic variations of the celiac plexus.

Diagnostic block of the celiac plexus often precedes (by 12 to 24 hours) therapeutic block. Exact location of the celiac ganglion and plexus is not critical in the former. Indeed, in an often-used technique for diagnostic block, the tip of the needle is placed in the correct fascial plane and fairly large volumes of local anesthetic are injected.[4] The rationale is that large volumes injected into the correct fascial plane will spread widely enough to block the celiac ganglia regardless of where they lie. Since weak local anesthetics are nontoxic, there is no reason not to inject large volumes. Therapeutic block of the celiac plexus, on the other hand, aims for permanent block by injection of neurolytic substances. In this block, exact location of the celiac plexus is important. The smallest possible amount of neurolytic substance should be injected because of its toxicity and because of the danger of possible damage to adjacent structures.

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The significance of the present observations lies more with therapeutic block than with diagnostic. In an effort to improve needle placement during therapeutic block of the celiac plexus, we studied the degree to which location of the celiac ganglia and plexus varies in relation to the celiac artery, to the anterior margin of the vertebral column, and to different vertebral levels. We also investigated whether the ganglia could be recognized and related to vertebral levels by computed tomography scans.

Methods and Materials

Ten female and 10 male adult bodies were studied. Twelve were embalmed and eight were studied at autopsy 2 to 12 hours after death.

The ages and causes of death of the individuals studied are given in Table 1. Although six patients had malignant disease, it did not involve the region of the celiac artery or the periaortic or retroperitoneal space. In all bodies, the thorax and abdomen were opened, and the greater splanchnic nerves were identified as they traversed the diaphragm and entered the celiac ganglia. The liver and stomach were removed; the origins of the celiac artery, the renal and adrenal vessels, and the aorta were left intact. The celiac ganglia were identified, and by careful dissection the peritoneum on the anterior surface of the ganglia was removed. Great care was taken not to disturb the celiac ganglia from the underlying fascia and thus to preserve the true anatomic relationship of the celiac ganglia to the posterior body wall. Microscopic sections were taken and examined to verify further that the structure identified was the celiac ganglion.

TABLE 1
Age in Years (average: 59), Sex, and Cause of Death of Patients Studied

Age	Sex	Cause of death
14	F	Congenital heart disease
22	F	Suicide
32	F	Carcinoma, breast
42	M	Suicide
45	M	Carcinoma, lung
50	F	Congenital heart disease
57	F	Leukemia
62	F	Leukemia
68	M	Myocardial infarction
70	M	Unknown
70	F	Ruptured left ventricle
71	M	Cerebrovascular accident
73	M	Complications of chronic obstructive pulmonary disease
74	M	Carcinoma, lung
75	M	Carcinoma, lung
76	M	Pneumonia
78	F	Myocardial infarction
79	M	Respiratory arrest
85	F	Cerebrovascular accident
86	F	Cerebrovascular accident

When the ganglia had been identified and demonstrated bilaterally, the number of ganglia present and the dimensions of the mass were recorded. Whether the left or the right ganglionic mass was dominant and whether the ganglia were cephalad or caudad to the celiac artery were determined.

A thread containing lead wire was sewn around the periphery of the right and left ganglia. A segment of lead wire was wrapped around the origin of the celiac artery. Anteroposterior roentgenograms of the abdomen were taken with the body supine. Right lateral roentgenograms were also taken. Whether the ganglia were superior or inferior to the vertebral bodies was determined from the anteroposterior roentgenograms. The vertebral level of the ganglia was assigned according to the vertebra that corresponded to the center of the ganglia. The distance from the center of the ganglia to the anterior margin of the vertebral bodies was determined from the lateral roentgenogram.

The records of five patients who had celiac plexus block to control pain associated with malignancy and who had computed tomography scans of the abdomen before receiving the block were reviewed retrospectively. The success of the block was determined and correlated with the anatomic features revealed by the scans.

Results

Table 2 shows that the vertebral level of the celiac ganglia in the 20 bodies studied tended to be lower

TABLE 2
Relation of Celiac Ganglia to Vertebral Column in 20 Bodies

Vertebral level of ganglia	Bodies with ganglia	
	Right side	Left side
Disk T-12 and L-1	5	3
Upper ⅓ L-1	5	3
Middle ⅓ L-1	3	4
Lower ⅓ L-1	4	6
Disk L-1 and L-2	3	3
Middle L-2	0	1

on the left than on the right. In 10 of 20 bodies, the ganglia on the left side were located opposite the middle or lower third of the first lumbar vertebra, and in 14 of 20, the ganglia on this side were below the middle third of the first lumbar vertebra. On the right side, the celiac ganglia were more evenly distributed, although in 10 of 20 bodies, the location was above the middle third of the first lumbar vertebra.

In Table 3, the number and dimensions of identifiable ganglia associated with the celiac plexus are given. The ganglionic mass on each side was most commonly oval in shape and was oriented obliquely, with one end close to the celiac artery and the other directed inferiorly and laterally. The number of ganglia on each side ranged from 1 to 5 but averaged 2.70 and 2.75 on the right and left sides, respectively.

Table 4 shows the vertebral level of origin of the celiac arterial trunk from the aorta and the relation of the celiac ganglia on each side of the bodies to it. Although the celiac artery varied considerably in size and length, a single arterial trunk was present in each instance. In all 20 bodies, the left celiac ganglia were inferior to the aortic origin of the celiac artery; on the right, all ganglia except one were inferior to the celiac artery. The average distance below the celiac artery was 0.6 cm on the right and 0.9 cm on the left.

Table 5 shows the relation of the celiac ganglia on the right and left sides to the anterior margin of the vertebral column as determined by lateral roentgenographic views. The left ganglia tended to be closer to the anterior vertebral margin; eight were less than 1 cm away. Overall, this relation was fairly consistent, since the distance was less than 1.49 cm in about 60% of the bodies. Furthermore, the ganglionic mass was less than 2.49 cm anterior to the vertebral column on the right in 18 of 20 and on the left in 19 of 20.

In the five patients who had computed tomography scans before celiac plexus block, three blocks were successful and two were unsuccessful. The celiac and superior mesenteric arteries could be visualized in the three successful blocks. In these subjects, a moderate

TABLE 3

Identifiable Ganglia and Dimensions of Ganglionic Mass in 20 Bodies

Ganglia on right side		Ganglia on left side	
No.	Dimensions (cm)	No.	Dimensions (cm)
4	4.5 x 2.5	5	1.7 x 2.0
3	3.0 x 1.4	2	2.0 x 1.0
2	2.5 x 2.0	2	2.5 x 1.5
3	1.5 x 0.7	1	2.2 x 0.8
2	2.8 x 1.5	3	2.4 x 2.3
2	2.4 x 0.8	2	4.0 x 1.9
2	2.4 x 1.3	3	2.0 x 2.5
3	1.5 x 2.0	4	2.0 x 3.0
3	2.0 x 1.0	2	2.5 x 1.5
2	3.0 x 0.5	3	2.0 x 2.0
1	1.5 x 0.8	3	2.5 x 1.9
1	1.4 x 1.3	2	2.2 x 1.6
4	4.0 x 3.0	3	2.0 x 3.0
4	3.5 x 2.0	3	3.5 x 2.0
3	3.5 x 2.0	2	2.0 x 2.0
2	3.5 x 0.6	2	2.2 x 1.2
3	3.5 x 1.0	3	2.4 x 2.0
3	2.5 x 1.5	3	2.2 x 1.3
3	2.2 x 1.2	4	3.0 x 1.5
4	4.5 x 1.5	3	2.5 x 1.5
Mean 2.70	2.79 x 1.43	2.75	2.39 x 1.83

TABLE 4

Superior and Inferior Relation of Celiac Ganglia to Celiac Artery in 20 Bodies

Vertebral level of celiac artery origin	Distance of ganglia above (+) or below (−) artery (cm)	
	Right side	Left side
Upper third L-1	+0.5	−1.5
Lower third T-12	−0.5	−0.1
Lower third T-12	−1.4	−2.1
Middle third L-1	−0.5	−3.0
Interspace T-12 and L-1	−0.2	0.0
Lower third L-1	−0.5	−0.5
Lower third T-12	−0.3	0.0
Upper third L-1	−0.8	−0.8
Middle third L-1	0.0	0.0
Lower third T-12	−1.0	−1.0
Lower third T-12	−1.0	−1.0
Lower third L-1	−0.5	−1.2
Lower third L-1	0.0	0.0
Interspace T-12 and L-1	−1.2	−1.0
Middle third L-1	−0.5	−0.5
Upper third L-1	−1.5	−1.5
Lower third L-1	−0.5	−1.0
Interspace T-12 and L-1	−0.5	−0.8
Lower third T-12	−0.8	−1.0
Interspace T-12 and L-1	−0.7	−1.2
Mean	−0.6	−0.9

TABLE 5

Relation of Celiac Ganglia to Anterior Margin of Vertebral Column in 20 Bodies

Distance of ganglia from margin (cm)	Bodies with ganglia	
	Right side	Left side
0 to 0.99	2	8
1 to 1.49	10	5
1.5 to 1.99	3	3
2.0 to 2.49	3	3
2.5 to 2.99	2	0
4.0	0	1

amount of retroperitoneal fat was present, and no retroperitoneal tumor was visualized. In the unsuccessful blocks, the celiac and superior mesenteric arteries were poorly visualized, and less retroperitoneal fat was present; periaortic retroperitoneal tumor could be identified.

Discussion

The source of fibers, the anatomic connections, and the distribution of the autonomic nervous system in the abdomen have been reviewed previously.[5-7] Briefly, the major part of the sympathetic system in the abdomen is the plexus of nerves extending along the front and sides of the entire length of the abdominal aorta. The upper and most dense part of the plexus lies on the sides and in front of the aorta at the level of the celiac artery and therefore is designated the "celiac plexus."

The celiac plexus contains preganglionic parasympathetic fibers, preganglionic and postganglionic sympathetic fibers, and afferent fibers. The preganglionic parasympathetic fibers are derived predominantly from the posterior vagal trunk. The postganglionic parasympathetic nerve cell bodies (and their axons) lie on or within the walls of the organ supplied. Preganglionic sympathetic fibers arising from T5-9 (or T-10) reach the celiac plexus through the greater splanchnic nerves, where they synapse with postganglionic sympathetic nerves. The collections of nerve cell bodies of the postganglionic sympathetic nerves form the celiac ganglia. The celiac plexus also receives postganglionic sympathetic fibers from the lumbar splanchnic nerves, the cell bodies of which are located in the upper one or two lumbar sympathetic ganglia. In addition, afferent fibers in the celiac plexus from abdominal viscera travel to the central nervous system by the same pathways that convey sympathetic efferent fibers (lumbar and thoracic splanchnic nerves). Within the plexus, individual nerves lose their identity, but structures supplied by the plexus receive an allotment of each type of nerve fiber. From the plexus, nerve fibers reach the upper abdominal organs primarily by accompanying blood vessels to the organs. Organs supplied include the stomach, liver, gallbladder, pancreas, adrenal glands, and kidneys.

The celiac plexus is not a separate and distinct structure but instead is arbitrarily established as the upper part of the plexus of autonomic nerves around the aorta. The celiac ganglia are enmeshed within the plexus. Because of the indistinct boundaries, considerable variation of the plexus in relation to a given vertebral level is expected and may be the reason why anatomy books frequently relate the position of the celiac ganglion to the celiac artery instead of to a specific vertebral level.[8-10]

Most techniques for blocking the celiac plexus rely on bony landmarks for placement of needles. The vertebral level at which the tip of the needle should be placed and the amount of drug injected vary considerably with the various techniques described for blocks of the celiac plexus. Some authors advocate that the needle tip be placed at the body of the 12th thoracic vertebra[11]; others recommend the interspace between T-12 and L-1[12]; while still others advocate the upper body of the first lumbar vertebra,[4,13] opposite the spinous process of the first lumbar vertebra,[14] at the anterolateral aspect of the body of the first lumbar vertebra,[15] or opposite the body of the first lumbar vertebra.[16-18] A celiac arteriogram has even been suggested in order to place the needle close to the celiac artery.[19] In addition to seeking the vertebral level, most techniques position the needle in such a way that the tip is from 1 to 1.5 cm anterior to the vertebral column.

The data presented here showing the celiac ganglia to be consistently anterior to the vertebral column suggest that those techniques advocating placement of needle tips anterior to the vertebral column should yield better blocks. Further, if a celiac arteriogram is used to position the needles in relation to the celiac plexus, our data suggest that the tips of the needles should be placed from 0.5 to 1 cm below the aortic origin of the celiac artery.

Fusion of sympathetic ganglia in adjacent body segments is known to occur. The incidence of fusion is high in the lower cervical and upper thoracic region, where a cervicothoracic (stellate) ganglion can be found in 82% of bodies.[20] Similarly, fusion of adjacent ganglia in the thoracic sympathetic trunk has been reported.[8] Fusion of lumbar sympathetic ganglia is suggested in this study by the differing numbers and sizes of ganglia found associated with the celiac artery. Further, the completeness with which adjacent ganglia fuse is probably important in determining the size of the celiac ganglia. Similarities in the total ganglionic mass and mean dimensions on the two sides indicate that the factors responsible for the fusion are similar bilaterally.

The present study indicates that the celiac ganglia vary considerably in size, in the number on each side, in total number, and in relation to any specific level of the vertebral column. Not only does the level of the ganglia on the two sides vary with respect to adjacent vertebral bodies but also the right and left sides are frequently at different levels, the ganglia on the left tending to be lower. The lower position of the left celiac ganglion contrasts with the general tendency for the left of paired abdominal organs, such as the kidneys and adrenal glands, to be located above the right. That one celiac ganglion on the left was located at the middle of the second lumbar vertebra emphasizes the extent to which the vertebral level of ganglia can vary. The vertebral level of the celiac ganglia in men was not different from that in women.

The celiac ganglia were enmeshed in an extensive network of dissectable nerve fibers in all bodies. We believe the ganglia represented the center of the celiac plexus; hence, techniques for blocking the plexus should attempt to position the needle tips near these ganglia. Because the ganglia are at different vertebral levels, techniques using right and left needles should result in more nearly precise placement of drug and better blocks irrespective of whether the block is being done for diagnostic or for therapeutic purposes.

Whether computed tomography scans can be used to identify the celiac ganglia and plexus before block procedures has not been established clearly. In this retrospective study, it was not possible to localize the celiac ganglia or relate them or the celiac artery to a vertebral level. In a prospective study, however, surface markers could be used, and the celiac artery and various vertebral levels could be related to the markers. Although the results of the present study are inconclusive, they do not exclude the possibility that in the future computed tomography may be useful in localizing the celiac artery and ganglia so that one can determine the best needle path to the area and whether the area is inaccessibly sealed off by tumor. Our review of the records of patients who had computed tomography scans just before celiac plexus block suggests that those patients with normal retroperitoneal anatomy and no metastatic tumor received the most successful blocks; thus, the scans might also be helpful in predicting successful blocks.

Based on anatomic variations of the celiac plexus and ganglia demonstrated in the study, the following conclusions can be made: (1) The different vertebral levels of the right and left celiac ganglia suggest that irrespective of whether block of the celiac plexus is to be diagnostic or therapeutic, a technique in which right and left needles are used should result in more nearly precise placement of drug and a better block. (2) The needle on the left should be placed so that the tip is at the level of the junction of the middle and lower thirds of the first lumbar vertebra, whereas that on the right should be placed approximately 1 cm higher. With this placement, the needle tip on each side should be in the center of the celiac plexus near the celiac ganglia. (3) Because the location of the celiac ganglia and plexus varies considerably in relation to a specific vertebral level, some unsuccessful blocks are certain to occur with techniques based on placement of needles according to predetermined bony landmarks.

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ANESTH ANALG
58:466–469, 1979

Impact of Propranolol on Hemodynamic Response and Blood Cyanide Levels during Nitroprusside Infusion: A Prospective Study in Anesthetized Man

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BEDFORD, R. F., BERRY, F. A., JR., AND LONGNECKER, D. E.: Impact of propranolol on hemodynamic response and blood cyanide levels during nitroprusside infusion: a prospective study in anesthetized man. Anesth Analg 58:466–469, 1979.

Ten patients receiving N_2O-morphine anesthesia for spinal fusion operations were given one or more doses of propranolol, 0.01 mg/kg IV, after an hour of nitroprusside (SNP) hypotension at a mean arterial pressure of 70 torr. During the hour before propranolol was administered, SNP dose requirement increased from 1.8 μg/kg/min ± 0.4 to 3.5 μg/kg/min ± 0.4 (mean ± SE, $p < 0.05$) and heart rate increased from 91 beats/min ± 3 to 108 beats/min ± 6 (mean ± SE, $p < 0.05$). Blood cyanide levels increased from a control value of 0.9 μM/L ± 0.2 to 7.2 μM/L ± 0.2 (mean ± SE, $p < 0.05$) and base excess decreased from −0.5 mEq/L ± 0.6 to −2.6 ± 0.4 (mean ± SE, $p < 0.05$).

Nine patients responded to propranolol with a significant ($p < 0.05$) reduction in heart rate (to 92 ± 9 beats/min) and nitroprusside requirement (to 1.8 ± 0.4 μg/kg/min, mean ± SE). No further increase in cyanide levels was observed, and base excess rose to −0.3 mEq/L ± 0.5 (mean ± SE, $p < 0.05$). One patient did not respond to a single dose of propranolol with a decrease in heart rate, and continued to require the same SNP dose (5.5 μg/kg/min). In this individual, blood cyanide levels increased from 6.8 μM/L to 9.6 μM/L during the hour after receiving propranolol, while base excess fell further, from −4.4 to −4.8 mEq/L.

Judicious administration of propranolol in a dose sufficient to lower heart rate during nitroprusside-induced hypotension reduces both the nitroprusside dose-requirement and also the likelihood of developing cyanide toxicity.

Key Words: SYMPATHETIC NERVOUS SYSTEM: sympatholytic agents, propranolol; ANESTHETIC TECHNIQUES, Induced hypotension: nitroprusside.

SODIUM NITROPRUSSIDE (SNP) is used widely to produce controlled hypotension despite the continuing concern about cyanide toxicity resulting from metabolism of the drug. Blood cyanide concentrations vary directly with the amount of SNP infused. Since resistance to SNP is often manifested by baroreceptor-mediated tachycardia, it has been suggested that propranolol might effectively reduce both heart rate and SNP dose requirement during deliberate

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hypotension.[1] Experiments in unanesthetized animals suggest that the addition of propranolol to vasodilator therapy reduces the dose requirement for the vasodilator, probably both by inhibiting renin release and by preventing the tachycardia associated with the hypotension.[2] This study was undertaken to determine the effects of propranolol on hemodynamic function, dose requirements for SNP, and blood cyanide concentrations during SNP-induced hypotension in humans.

Methods

Ten consecutive patients scheduled for Harrington rod spinal fusion operations using deliberate hypotension and an intraoperative awakening technique were the subjects of this investigation. They ranged in age from 8 to 18 years (mean = 13) and weighed between 18 and 105 kg (mean = 56). The protocol for the study was approved by the University of Virginia Medical Center committee for the protection of human subjects in research.

Premedication consisted of morphine, 0.1 mg/kg, and atropine, 0.4 mg, intramuscularly 1 hour prior to arrival in the operating room. General anesthesia was induced with a thiopental-N_2O-O_2 sequence. All patients were paralyzed with d-tubocurarine; their tracheas were intubated and artificial ventilation was maintained throughout the operation. Additional morphine was administered intravenously to a total mean dose of 0.4 ± 0.02 mg/kg (mean ± SE). After insertion of arterial and central venous cannulae, patients were placed in the prone position and baseline values for mean central venous and arterial blood pressure and heart rate were recorded. Central venous and arterial blood gas tensions were measured and arterial blood was obtained for cyanide determination.

The protocol consisted of 1 hour of induced hypotension (to a mean arterial pressure of approximately 70 torr) produced by SNP infusion alone, followed by an intravenous bolus of propranolol, 0.01 mg/kg IV, and an additional hour of hypotension at the same arterial pressure by continued SNP infusion. Hemodynamic function, namely central venous pressure (CVP), mean arterial pressure (MAP), and heart rate (HR) were measured continuously and these, plus SNP dose requirement, were tabulated at 15-minute intervals for 1 hour before and 1 hour after intravenous propranolol. Two patients whose heart rates did not respond to a single intravenous injection of propranolol were given one and two additional doses of propranolol (0.01 mg/kg), respectively. Arterial and central venous blood gas tensions were determined after 1 hour of SNP infusion (immediately before propranolol was given) and again after the 2nd hour of SNP infusion. Arterial blood was also obtained at these times for cyanide determinations using the spectrofluorometric technique of Rodkey and Collison.[3] The data were analyzed by analysis of variance and/or Duncan's multiple range test; $p < 0.05$ was regarded as significant.

No additional morphine or curare was given during the 2-hour study. Blood and intravenous fluids were replaced as needed to maintain a constant central venous pressure. Surgical stimulation remained reasonably constant throughout the study and intraoperative awakening did not occur until 1 to 2 hours after the study was completed.

Results

One patient in this series (the youngest) did not respond with a reduction in either heart rate or SNP requirement following a single dose of propranolol, 0.01 mg/kg. Heart rate remained at 120 beats/min and the SNP infusion rate had to be maintained at 5.5 μg/kg/min throughout the study. Blood cyanide concentrations in this patient increased from a control value of 0.7 μM/L to 6.8 μM/L after 1 hour, and then to 9.6 μM/L after 2 hours of SNP. Base excess decreased from zero to −4.4 mEq/L at 1 hour and −4.8

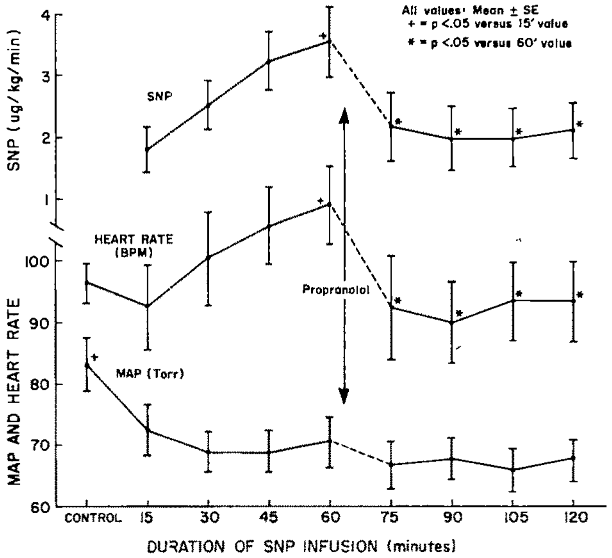

FIG 1. Mean nitroprusside (SNP) requirement, heart rate, and arterial pressure in the nine patients who responded to propranolol. Heart rate and SNP dose-requirement increased significantly over initial values by the end of the 1st hour of hypotension prior to propranolol. Propranolol caused prompt and significant reductions in these parameters, which then persisted throughout the 2nd hour of the study.

mEq/L after 2 hours of SNP. This was the fourth patient in the series and the first to demonstrate that a single dose of propranolol, 0.01 mg/kg, might be insufficient to control tachycardia and avoid excessive cyanide levels during SNP infusion. Accordingly, in two subsequent patients who did not respond to propranolol initially, the dose was repeated at 5-minute intervals until a reduction in heart rate was observed. One patient required a single propranolol supplement; the other required two supplements.

Fig. 1 summarizes our findings with regard to SNP infusion rates and hemodynamic function in the other nine patients. During the hour before propranolol was administered there was a significant increase in heart rate which was accompanied by a significantly increased dose requirement for SNP. After propranolol, the SNP dose requirement decreased significantly to 56% (± 8% SE) of that after 1 hour of SNP, and heart rate was reduced to 82% of that observed before propranolol. These values were essentially the same as those observed during the first 15 minutes of SNP infusion.

Among the nine patients who responded to propranolol with a reduction in both heart rate and SNP dose requirement no further increase in cyanide level occurred. Base excess increased significantly after propranolol as compared with values obtained immediately before propranolol was given (Fig. 2). Arterial and central venous P_{O_2}, and P_{CO_2} values did not change significantly during the study.

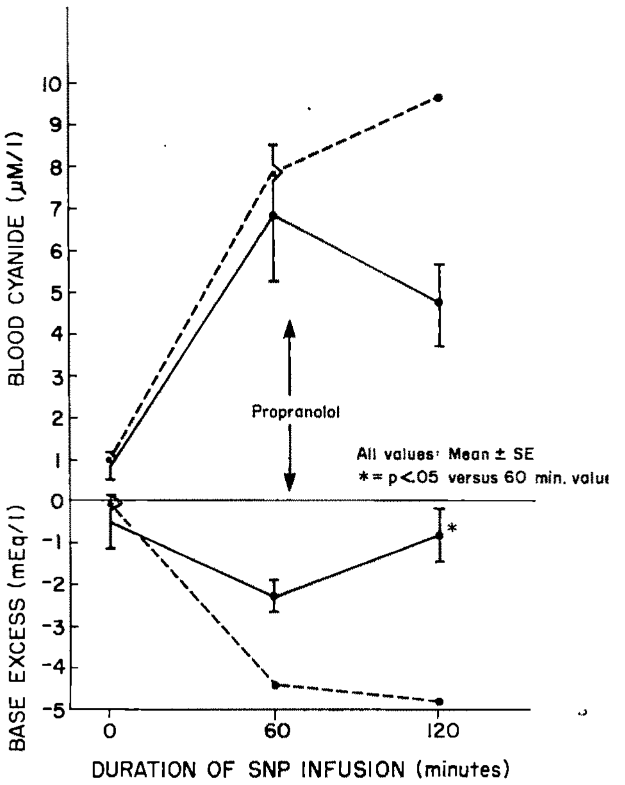

FIG 2. Blood cyanide increased and base excess decreased in all patients during the 1st hour of SNP infusion. Broken line indicates values observed in the one patient who did not respond to a single propranolol dose. In patients whose heart rate decreased after propranolol, there was no further increase in cyanide level, and mean base excess was significantly higher as compared with the pre-propranolol value.

Discussion

This study indicates that propranolol, when given during SNP-induced hypotension in a dose sufficient to lower heart rate, causes a reduction in SNP dose requirement and prevents further increases in cyanide levels. The one patient in this series who did not receive enough propranolol to lower heart rate had an increase in cyanide concentration when SNP infusion rate remained constant during both the 1st and 2nd hours of study, a finding consistent with our previous observations of cyanide levels during constant SNP infusion.‡

Cottrell et al[4] have shown that cyanide toxicity resulting from SNP infusion can be avoided by pretreatment with hydroxocobalamine. It is our feeling, however, that for clinical purposes minimizing production of cyanide by reducing SNP dose-requirement makes more sense than does treatment of toxicity.

Propranolol augments the effect of SNP by at least two mechanisms: (1) a reduction in cardiac output, which accompanies the observed reduction in heart rate,[5] and (2) a decrease in plasma renin activity, which is markedly elevated during SNP infusion.[6]

All 10 patients demonstrated an increase in heart rate during the 1st hour of nitroprusside infusion, and propranolol appears to be particularly useful in counteracting this response during N_2O-morphine anesthesia. Heart rate tended to slow gradually over several minutes after propranolol administration, thus allowing for gradual reduction in SNP infusion rate while maintaining a reasonably constant level of arterial hypotension. None of the patients exhibited severe bradycardia or hypotension after propranolol administration.

It is possible that the improvement in acid-base status observed after reduction in SNP infusion rate may not have been related to lower blood cyanide values. Although no bicarbonate was given, it is possible that some of the citrate given in blood transfusions could have been metabolized to bicarbonate with a resultant increase in base excess.

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‡ McHugh RD, Longnecker DE, Berry FA, et al: Metabolic changes and cyanide concentrations during deliberate hypotension with sodium nitroprusside. Abstracts of Scientific Papers—1978 American Society of Anesthesiologists Annual Meeting, pp 525–526.

Potential risks of judicious propranolol administration during general anesthesia and SNP infusion seem minimal. Pretreatment with oral propranolol prior to myocardial revascularization prevents tachycardia but does not otherwise appear to alter anesthetic management for this operation,[7] and intravenous propranolol administered to dogs during enflurane,[8] halothane,[9] or nitrous oxide[9] anesthesia causes only minimal hemodynamic changes. Propranolol given to dogs before SNP infusion during 0.6% halothane limited tachycardia and lowered cardiac output, whereas the arterial pressure response to SNP infusion was essentially unchanged.[5]

In summary, intravenous propranolol administered during SNP-induced hypotension significantly reduced the dose requirement for SNP. This technique affords precise control of blood pressure and also helps to minimize the risk of developing cyanide toxicity.

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Enzyme Induction

The toxicity and metabolism of methoxyflurane were compared in Fischer 344 rats pretreated with phenytoin or phenobarbital. Treatment with either drug potentiated the polyuric effects of methoxyflurane by more than 100%. Also, serum inorganic fluoride (F^-) levels and urinary F^- excretions after methoxyflurane exposure were comparable in phenytoin- and phenobarbital-treated rats, a 26 to 49% increase as compared to rats treated with methoxyflurane alone. In vitro, 10-fold increases in the rate of hepatic microsomal methoxyflurane defluorination were observed after treatment of rats with either phenytoin or phenobarbital. Defluorination of three additional fluorinated ether anesthetics, enflurane, isoflurane, and sevoflurane, also was examined in vitro. Phenytoin and phenobarbital treatment resulted in similar enhancement of defluorination of the latter two anesthetics, but not enflurane. Phenytoin and phenobarbital treatment increase defluorination of fluorinated ether anesthetics to approximately the same extent in vitro and in vivo in Fischer 344 rats. *Caughey GH, Rice SA, Kosek JC, et al: Effect of phenytoin (DPH) treatment on methoxyflurane metabolism in rats. J Pharmacol Exp Ther 210:180–185, 1979)*

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Can the Extent of Halothane Debromination Be Predicted Preoperatively?

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DUVALDESTIN, P., MAZZE, R. I., NIVOCHE, Y., AND DESMONTS, J.-M: Can the extent of halothane debromination be predicted preoperatively? Anesth Analg 58:470-474, 1979.

In an attempt to predict the extent of halothane debromination, antipyrine metabolic clearance rate was measured preoperatively in 22 surgical patients, then correlated with percent hours of subsequent halothane exposure and postoperative serum bromide levels. There was a significant correlation ($r = 0.78$, $p < 0.001$) between peak bromide level and anesthetic exposure but no correlation between peak bromide levels and antipyrine metabolic clearance rate. Thus, antipyrine is of no value for predicting the extent of halothane debromination. Mean peak bromide level 0.97 ± 0.09 mM occurred on day 3 after anesthesia. This value is well below the psychoactive range. The data, therefore, also suggest that there is not a causal relationship between halothane biotransformation and the clinical syndrome of bromism.

Key Words: ANESTHETICS, Volatile: halothane; IONS: bromide; BIOTRANSFORMATION (DRUG): halothane.

BIOTRANSFORMATION of halothane to toxic metabolites has long been considered a possible cause of the occasional case of hepatic necrosis which follows its administration. More recently it was suggested that bromism might develop as a consequence of halothane administration.[1,2] Thus, it would be of value to be able to predict, preoperatively, the extent of halothane debromination likely to occur in surgical patients. Halothane biotransformation is mediated by the hepatic microsomal drug metabolizing enzyme system, with 1 mole of bromide evolving from each mole of biotransformed halothane.[3-5] In man, antipyrine has been extensively employed to assess the in vivo rate of activity of this system.[6-10] A highly sensitive method of bromide analysis, x-ray fluorescence spectrometry,[11,12] now permits more accurate measurement of serum bromine levels and, hence, assessment of the degree of halothane debromination than has been possible in previous studies.[1,13,14] In the present study of 22 surgical patients, preoperative antipyrine metabolic clearance rate and percent hours of halothane exposure (ie, the concentration of halothane, in percent, multiplied by the duration of administration, in hours) were correlated with peak serum bromide levels to evaluate the suitability of the use of antipyrine to predict the extent of halothane debromination.

Methods

Twenty-two patients without cardiovascular, renal,

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or hepatic disease, scheduled for otologic (n = 18) or orthopedic (n = 4) surgical procedures were included in the study. There were seven female and 15 male subjects; mean age (± SE) was 29.0 ± 2.6 years. Informed consent was obtained from all subjects. Patients were accepted for study only if it was thought that intraoperative blood transfusion would not be necessary and intravenous fluid therapy would not be required for more than 8 hours after operation. All subjects denied use of drugs, although several smoked cigarettes and drank alcoholic beverages.

No sedation was given the night before operation. Atropine, 0.5 mg, and droperidol, 5 to 15 mg, were given intramuscularly approximately 1 hour before arrival in the operating room. General anesthesia was induced with thiopental, 4 to 10 mg/kg, and succinylcholine, 1 mg/kg, was used to facilitate endotracheal intubation. Halothane, 0.2 to 0.5%; phenoperidine, 3 to 10 mg, a short-acting, synthetic narcotic; and 60% nitrous oxide with 40% oxygen were administered for maintenance of anesthesia. End-tidal gas samples were obtained every 15 minutes and halothane concentration was measured with a Varian 1400 gas chromatograph. Anesthetic exposure was expressed in percent hours, ie, the concentration of halothane, in percent, multiplied by the duration of administration, in hours.

Twenty-four hours before administration of premedication, subjects received a single oral dose of antipyrine, 15 mg/kg. This treatment is not known to alter halothane metabolism. Salivary samples were obtained for antipyrine analysis by voluntary expectoration before and 3, 5, 7, 9, 11, 13, and 24 hours after antipyrine ingestion. This method of sampling is more acceptable to subjects than is repeated venipuncture and salivary antipyrine levels in our laboratory (P. Duvaldestin, unpublished data) and in other laboratories[7, 9, 10] correlate closely with plasma values. Samples were centrifuged to remove particulate matter and the supernatant was frozen for subsequent analysis using the gas-liquid chromatographic method of Prescott et al.[15] as modified by Miguet et al.[16] Antipyrine pharmacokinetics were calculated assuming a one-compartment open model. Antipyrine half-life (t½) was calculated by least squares regression analysis of the exponential decline of antipyrine concentration with time. The apparent volume of antipyrine distribution (aVd) was calculated as $aVd = I/C_0$, where I is the amount of antipyrine ingested and C_0 the concentration extrapolated to time zero. The metabolic clearance rate of antipyrine was calculated from the formula, clearance = $(0.693 \cdot aVd)$t½.

Venous blood samples (15 ml) for bromide analysis were obtained before anesthesia and daily for 9 days after anesthesia from the first six patients studied. Since peak, or near peak, bromide levels occurred on day 3 in each of these subjects, postanesthesia samples were collected only on days 1, 3, and 8 from the remaining 16 patients. Samples were allowed to clot, then they were centrifuged and the serum was frozen for subsequent analysis. Bromide levels were determined directly on serum by x-ray fluorescence spectrometry, as previously reported.[11, 12] This method measures total bromine rather than bromide ion. However, in previous studies,[12] we determined that 12 to 24 hours after exposure to halothane, more than 95% of bromine in serum is in the form of bromide ion.

The dependence of peak serum bromide level on the independent variables, halothane exposure and antipyrine metabolic clearance (or t½) were analyzed by multiple regression analysis with logarithmic transformation of the several variables; $p < 0.05$ was considered statistically significant.

Results

Standard bromide curves were linear from 0 to 10 mM. At concentrations below 100 nM it was possible to distinguish between samples with bromide differences as small as 10 µM. Mean serum bromide values (± SE) after halothane anesthesia are shown in Fig 1; peak values occurred 3 days after administration and were 0.97 ± 0.09 mM; the range of individual peak values was 0.35–1.92 mM. Bromide values for one of the patients whose serum was sampled each day are shown in Fig 2. Bromide t½ in this individual was 14.0 days; the mean t½ for all subjects was 12.8 ± 1.1 days with a range of 5.3–23.0 days. Mean halothane expo-

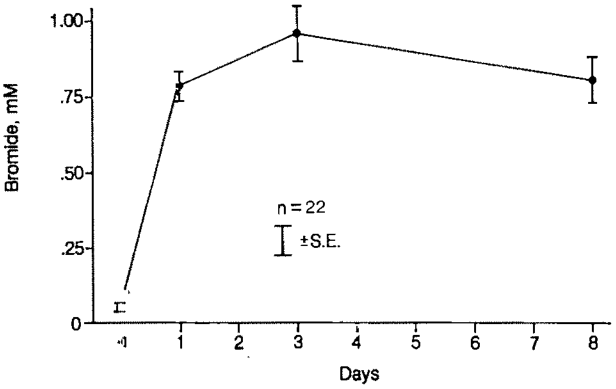

FIG 1. Mean serum bromide levels (± SE) at various sampling intervals. Bromide levels peaked on day 3 after anesthesia and gradually declined thereafter.

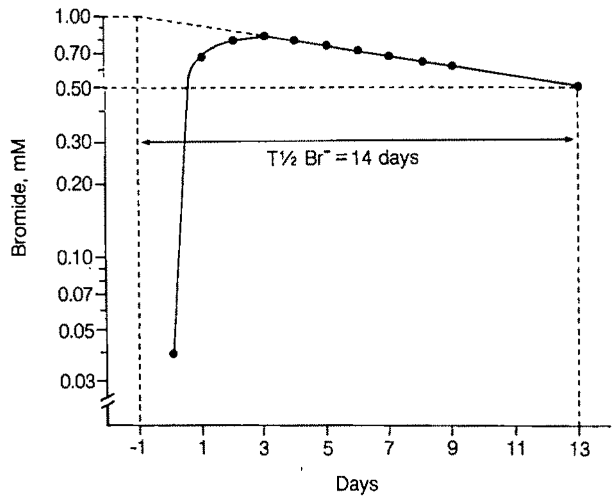

Fig 2. Individual serum bromide levels in a patient from whom blood samples were obtained daily for 9 days and on day 13 after anesthesia. Bromide t½ was 14 days. Mean bromide t½ (± SE) for all subjects was 12.8 ± 1.1 days.

TABLE

Antipyrine Pharmacokinetic Data

	Metabolic clearance	t½	Apparent volume of distribution
	ml/min/m²	*hr*	*L*
Mean ± SE	34.3 ± 2.0	9.1 ± 0.5	41.1 ± 2.0
Range	55.6–21.3	14.6–4.7	58–23

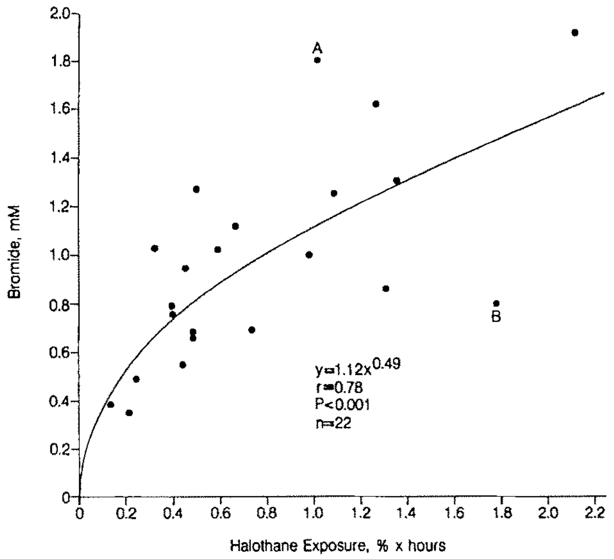

Fig 3. Peak serum bromide levels following halothane anesthesia. The experimental data best fit a power curve with the equation $y = 1.2x^{0.49}$. Antipyrine metabolic clearance for subject A, furthest above the line of best fit, and subject B, furthest below the line, were virtually identical; values were 26.7, and 27.0 ml/min/m², respectively.

sure was 0.77 ± 0.11% hours with a range of 0.15–2.11% hours. Mean duration of anesthesia was 3.5 ± 0.4 hours with a range of 1.3 to 9.0 hours. Mean values for antipyrine metabolic clearances, t½ and *aVd* are presented in the Table.

The simple correlation between peak serum bromide concentration and halothane exposure is best described by a power curve (Fig 3); the equation defining the best fitting curve is $y = 1.12X^{0.49}$ ($r = 0.78$; $p < 0.001$). There was no correlation between peak serum bromide and antipyrine metabolic clearance ($r = 0.04$; $p > 0.5$). The multiple correlation of peak serum bromide on halothane exposure and antipyrine clearance was 0.62. This compared to $r^2 = (0.78)^2 = 0.61$ for the simple correlation of peak serum bromide on halothane exposure suggesting that virtually all of the dependence of bromide level on the two independent variables was due to halothane exposure. Examination of individual data from patients with extreme values provided little additional information. Antipyrine metabolic clearance for subject A, furthest above the line of best fit in Fig 3 and subject B, furthest below the line, were virtually identical; values were 26.7, and 27.0 ml/min/m², respectively. Also, the two patients with the highest (55.6 ml/min/m²) and the lowest (21.3 ml/min/m²) antipyrine clearances, had peak bromide levels in close agreement with predicted values. There was no correlation between peak serum bromide level and body surface area ($r = 0.09$; $p > 0.4$) or body weight ($r = 0.11$; $p > 0.4$). Finally, results were essentially the same when data were analyzed using antipyrine t½ as the pharmacokinetic variable rather than antipyrine metabolic clearance rate or duration of halothane administration rather than percent minutes.

Discussion

The results of the present study indicate that the extent of halothane debromination cannot be predicted preoperatively using antipyrine metabolic clearance rate as an indicator of an individual's capacity for hepatic drug metabolism. Although there was a highly significant correlation between exposure to halothane and peak serum bromide level, there was no relationship between antipyrine clearance and bromide concentration.

What is the reason for this lack of correlation? One possibility is that antipyrine is not an appropriate compound for measurement of the in vivo rate of hepatic drug metabolism in man. However, antipyrine has had wide usage in clinical pharmacologic studies for just this purpose.[6-10] Antipyrine is rapidly distributed in total body water, is minimally bound to plasma proteins, and is metabolized, almost exclusively, by hepatic mixed function oxidase systems. Its metabolism is not influenced by hepatic blood flow. The only rate-limiting step in the disposition of antipyrine is its metabolism by hepatic mixed function oxidase enzymes. In spite of its many suitable properties, antipyrine still might not be an appropriate indicator of halothane metabolism if its biotransformation and that of halothane occurred via different pathways. However, the primary pathway for antipyrine metabolism involves a hydroxylation reaction[17] and, although two different metabolic pathways for halothane biotransformation have been proposed, most evidence indicates that the predominant pathway for aerobic halothane metabolism also involves hydroxylation.[5, 18, 19] It is likely that the major limitation of antipyrine pharmacokinetic measurements for predicting halothane debromination relates to the large quantitative differences in drug metabolism that occur among individuals. Although the extent of biotransformation of a compound by any one person or by pairs of identical twins is relatively constant from time to time, quantitative differences in biotransformation among genetically and environmentally dissimilar individuals at a given time may be very great.[8, 17, 20] An excellent example of this is seen in studies of anesthetic biotransformation, where 2- to 4-fold variations in halothane,[12, 20] methoxyflurane,[21-23] and enflurane[14, 24] biotransformation are common among subjects exposed to approximately the same anesthetic dose. In the few instances where anesthetic metabolism data for identical twins have been reported[14, 20] or where one individual has been anesthetized on more than one occasion,[25] there has been remarkable quantitative agreement among the different measurements. Antipyrine, then, is a convenient and sensitive tool for examining hepatic microsomal function, provided that each subject serves as his or her own control, thereby increasing the sensitivity and power of the test.[17, 26]

The present study also allows examination of the relationship of halothane administration to the development of bromism. In reports of bromism unrelated to anesthesia, early signs such as somnolence and confusion are first seen at serum bromide levels of 6 to 12.5 mM.[27-29] In the present study peak bromide levels as high as 6 mM were not found nor were they present in any of the four previous halothane studies in which bromide measurements were made.[1, 13, 14, 30] The time course of the rise in serum bromide after anesthesia also is relevant to understanding the possible relationship of bromism to halothane administration. Immediately after anesthesia bromide levels rarely exceed 0.5 mM, and on the first postanesthetic day values usually approximate 1.0 mM.[1, 13, 14, 30] Higher levels may be observed late in the postanesthetic period. In two studies of prolonged halothane anesthesia in volunteers,[13, 14] mean peak bromide levels occurred 2 to 6 days after anesthesia and were in the range of 3.0 mM; the highest individual value was 4.2 mM. Thus, it is unlikely that psychoactive bromide levels will result from halothane administration.

Why then the concern regarding bromism following halothane administration? In the report of Tinker et al,[1] the patient with the highest bromide level, 2.4 mM, was comatose for 9 days after operation; his gradual return to consciousness coincided with declining serum bromide levels. In an accompanying editorial,[2] the case was referred to as an example of prolonged sedation following halothane anesthesia. However, this patient had a lengthy intracranial operation for a cerebral aneurysm and his serum bromide level on the first postoperative day was only about 1.0 mM. On the fifth postoperative day the serum bromide level peaked at 2.4 mM, a value still less than half the minimum concentration thought to be psychoactive. We believe that a much more likely explanation for the patient's prolonged coma was altered cerebral function secondary to surgical trauma. In light of the low bromide levels seen immediately following anesthesia[1, 13, 14, 30] it is unlikely that halothane biotransformation to bromide will lead to early postoperative somnolence or to failure to regain consciousness.

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Psychomotor Performance following Exposure to Trace Concentrations of Inhalation Anesthetics

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Using three psychomotor tasks administered three times each at 2-week intervals, we studied the performances of 18 control subjects and 18 subjects who were routinely and daily exposed to trace concentrations of anesthetic gases in the course of their clinical practice. No significant differences attributable to exposure to trace concentrations of anesthetics were detected. It is concluded that laboratory studies may overestimate the degree of alteration of psychomotor skills associated with exposure to trace concentrations of inhalation anesthetics.

Key Words: ANESTHETICS, Volatile: trace concentrations; ANESTHETICS, Gases: trace concentrations; PSYCHOLOGIC RESPONSES: trace concentrations.

A SUSPECTED increase in the incidence of a variety of health-related problems among operating room (OR) personnel has been said to be linked to chronic exposure to trace quantities of anesthetic gases which escape into the open OR atmosphere.[1] These trace concentrations may also have more immediate deleterious effects upon CNS activity, and a particular issue of concern involves the extent, if any, to which the psychomotor responsivity of OR personnel may be slowed or otherwise disrupted by inhalation of these gases.[2-5]

Evidence that psychomotor functioning may indeed be significantly impaired by inhalation of anesthetic gases in trace quantities comes largely from controlled laboratory studies in which the introduction of minimal amounts of various anesthetic agents into the inspired air provided to volunteer subjects has proven sufficient to impair subsequent performance on a variety of psychomotor tasks.[3, 4, 6] It should be noted, however, that the dissimilarity between the conditions found in these studies and those that exist in the natural OR environment makes uncertain the degree to which the results of the former can be generalized to clinical conditions. For example, use of breathing masks or tents to ensure that subjects receive a steady flow of a predetermined level of anesthetic gas in the experimental studies imposes several hours of idleness and relative immobility upon the subjects just prior to psychomotor assessment. The possibility exists that the performance decrements seen stem not from the inhalation of small amounts of anesthetic gas alone, but rather from an interaction between the low levels of gas inhaled and the preceding hours of relative inactivity. More important, perhaps, is the fact that personnel in an OR, unlike subjects in a laboratory study, are seldom, if ever, likely to experience prolonged exposure to nonfluctuating levels of any anesthetic gas or gas mixture. Variations in the nature and duration of surgical procedures, variability in the efficiency of ventilating systems, OR air turnover changes produced by uncontrolled ingress and

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egress, and an individual's own movement and technique around the gas sources are some of the factors making it unlikely that air inspired in the OR contains a constant amount of anesthetic gas over a prolonged time span.

The degree of psychomotor impairment produced in a laboratory study, then, may or may not estimate well the degree of impairment, if any, occurring under the more variable conditions of the OR. A further contribution to the uncertainty regarding the generalizability of experimental study results is the fact that subjects, typically serving as their own controls in a cross-over experimental design, are exposed to anesthetic gas on only one occasion. This once-only exposure precludes assessment of the degree to which a tolerance for small amounts of anesthetic gas might develop, or, conversely, assessment of the possibility that some degree of heightened sensitivity to the presence of trace agents might result from repeated exposure.

The present study was undertaken to assess over time the psychomotor skills of individuals exposed daily and routinely to trace concentrations of anesthetic gases, and thereby to establish more clearly the degree of risk present in the actual OR environment.

Method and Procedure

Subjects

Thirty-six male medical students, representing experimental and control groups of equal size, were the subjects in the present study. There was an insufficient number of female students available to meet the requirements of the present experimental design.

The experimental group (E) consisted of students taking an elective clerkship in anesthesiology. The control group (C) was comprised of volunteers from among the medical students taking the psychiatry clerkship. Excluded from the study were students who had just completed a clerkship involving significant time in the operating room (e.g., surgery) or who had had an anesthetic as a patient within the last year. All students who volunteered to serve as subjects in the present study provided informed consent consistent with both federal and institutional guidelines and procedures concerning research involving human subjects.

Assessment Methods

All subjects were assessed on three occasions, 2 weeks apart, over a 4-week period with a selected battery of three psychological tests. The battery was comprised of two tests, Finger Tapping and Grooved Pegboard, that are often a part of a standardized neuropsychological battery.[7] The third test was the Rotary Pursuit Apparatus (Lafayette Instrument Co, model 2203). These tests were selected to assess attention, concentration, manual dexterity, coordination, and reaction time, aspects of performance that previous investigators[4] have found to be affected by exposure to trace concentrations of anesthetic gases under laboratory conditions.

Finger Tapping. This test, which utilizes a key with attached calibrated counter, is a measure of finger tapping speed. The index finger of the preferred hand is used first, then that of the other hand. The subject is given five consecutive 10-second trials with the hand held in a constant position to assure that movements of only the finger rather than the whole hand and arm were required. Every effort is made to encourage the subject to tap as fast as possible. This test evaluates motor speed.

Scoring is based on the mean score for five consecutive trial scores within a range of 5 points. If these are not obtained, then the test is discontinued after ten trials, and a mean is computed from the five trial scores which best reflect maximum performances. Each subject obtains a score for his dominant and nondominant hand.

Grooved Pegboard Test. This test consists of a 10-cm^2 pegboard which has five rows and five columns of slotted or grooved holes into which similarly grooved pegs are to be placed in row sequence from top to bottom. The subject first places the pegs with his dominant hand; the second trial is with his nondominant hand. Scoring is the total time to complete the task, and scoring is separate for each hand. This test primarily tests manual dexterity.

Rotary Pursuit Apparatus. This test requires complex hand-eye coordination in placing and keeping a hand-held stylus in contact with a rotating disc. The equipment used in the present study provided for automatic timing for target contact per 20-second trial with the time scores seen only by the experimenter. For the present study the disc was rotated at 45 and 60 rpm for two trials each in a counterbalanced sequence (ABAB or BABA) with 20 seconds between trials.

Procedure

Each subject was tested by one of four trained psychology technicians who were randomly assigned to the subjects. Each testing session lasted approximately 20 minutes. The order of presentation of the three tests was completely counterbalanced; thus, none of the subjects received the tests in the same order over the three testing sessions.

The subjects in the experimental group were tested on the 1st day of their clerkship prior to exposure to the atmosphere in the OR suites. Two weeks later, and then 4 weeks after the initial assessment, they were assessed on exiting the operating room complex. The subjects in the control group were assessed shortly after their orientation period, and as close as possible to the prescribed times as their schedules would allow.

Table 1 shows the average time in days between testing occasions for Groups E and C. The shorter time for the subjects in the experimental group on the final testing session reflects the fact that most of the subjects were taking a 4-week clerkship, and, hence, testing was accomplished on the last full day in the operating room suite prior to the weekend which would conclude the clerkship. While there are statistically significant differences between the groups on each occasion, pragmatically the times are similar and acceptable for further analyses of group results.

TABLE 1

Average Time in Days between Testing Sessions for Groups E and C

Group	Baseline–2 weeks	Baseline–4 weeks
E	$\bar{X} = 14.00$ Range = 13–16	$\bar{X} = 26.16$ Range = 24–28
C	$\bar{X} = 15.22$ Range = 14–17	$\bar{X} = 30.16$ Range = 27–34

Assessment of Operating Room Atmosphere

The subjects in the experimental group were assigned to one operating room, in which they spent 90% of their time. Previous investigators have shown that areas of high concentration of trace gases exist around the anesthetic machine, the head of the patient, and at the level of the anesthetist; therefore, this area was selected to obtain samples for measurement of concentrations of anesthetic gases.

The type of scavenging system used for this room was a gravity-type system[8] which vented the gases from the over-flow valve of the anesthesia machine via conductive corrugated rubber hose, measuring 117 cm in length and 2.5 cm in diameter, to the floor. The anesthetic machine was an Ohio Heidbrink series 2000 fitted with a stem valve seated on a stainless steel orifice providing positive opening and closing pressure. The "O" ring seals were designed to prevent waste gas leakage into the room. Excess gases were conducted to a distance 10 cm above floor level and 165 cm from the exhaust vent of the non-recirculating air conditioner system. The room volume was 312 m^3. It had an air ventilation of 60.43 m^3/min and an air-exchange rate of 0.32/min. Air inflow to the room was via two vents located in the ceiling (one directly above the patient's head) and outflow was via a wall vent directly behind the head of the operating table. The intake and exhaust flows were continuously monitored during the entire testing period.

All anesthetics were administered using a semi-closed circle technique with masks or endotracheal tubes and manually assisted or controlled ventilation. No attempt was made to standardize the teaching methods of the staff or resident instructors assigned to the room, so some utilized the "empty-the-bag" technique before extubation and prior to oxygenation of the patient, i.e., detaching the breathing bag from the machine. This act was, however, the exception rather than the rule.

A plunger type sample of air was obtained according to the instructions from the Boehringer Laboratories manual with the cartridge then sealed tightly and placed in a mailable, leak-proof container. The sampling tube was made of impact-extruded dense aluminum and had a capacity of 150 ml. It had undergone 538 C flash cleaning before use. The samples then underwent chromatographic analysis at the Boehringer Laboratories. They employ a Varian gas chromatograph (model 27680) and report accuracies of ±1 ppm for nitrous oxide, and ±0.05 ppm for halothane.

To obtain gas samples for analysis of a steady-state contamination, "grab" samples were taken from the area 45 cm between the patient's face and the machine, at the level of the over-flow valve. Samples were taken either 30 minutes after induction of anesthesia (N = 17), or within 30 minutes of the completion of the last case on a given day (N = 18). This information covered two peak levels, i.e., during induction and an accumulated level during a surgical day.

Results

Air Samples

The atmosphere of the OR was sampled as previously described on 35 occasions. This sampling spanned a 17-month period during which the subjects in the experimental group rotated sequentially through the anesthesiology elective with minimal overlap in assignments. On 30 occasions nitrous oxide in amounts ranging from 3-2334 ppm ($\bar{X}$ = 374.87 ppm) was found, 12 times as the single agent present, 16 times in combination with halothane in amounts ranging from 0.2 to 36.9 ppm ($\bar{X}$ = 4.55 ppm), and twice in combination with enflurane in amounts of 0.3 and 4.6 ppm. Cyclopropane (38.8 ppm) was the sole agent present once. On four occasions no trace anesthetic gases were detected. While there was marked variability in the levels of gases found in these samples, this variability was evenly distributed across the data collection period. That is, no clustering of high or low gas values occurred at any given time during the sampling period, and the composition of the OR atmosphere, while variable, was similar in its variability for all subjects in the experimental group.

Of the 35 air samples 23 were taken on either Mondays (n = 12) or Fridays (n = 11), as virtually all psychomotor assessment at the 2- and 4-week periods was done as the subjects finished working in the OR on these days. Illness and holidays kept two subjects out of the OR on the Monday or Friday of the weeks in which they were to be assessed, and hence they were tested upon leaving the OR on alternate days in those same weeks.

The amounts of nitrous oxide found in the Monday samples ranged from 0 (on three occasions) to 2334 ppm ($\bar{X}$ = 559.66 ppm). The amounts of halothane found in the Monday samples ranged from 0 (on five occasions) to 36.9 ppm ($\bar{X}$ = 4.23). In the 11 Friday samples, nitrous oxide was found in amounts ranging from 0 (on two occasions) to 1232 ppm ($\bar{X}$ = 244.91 ppm), and halothane was found in amounts ranging from 0 (on seven occasions) to 10.6 ppm ($\bar{X}$ = 1.11). The remaining 12 air samples were distributed over Tuesdays, Wednesdays, and Thursdays. In them, nitrous oxide was found in amounts ranging from 4-960 ppm ($\bar{X}$ = 153 ppm), and halothane was found in amounts ranging from 0 (on seven occasions) to 3.7 ppm ($\bar{X}$ = 0.85 ppm).

The gas levels found in the present study are comparable to the levels of nitrous oxide and halothane reported by Gamberale and Svensson[2] in their study of ORs in five Swedish hospitals, and for the most part surpass, particularly on the days when almost all of the psychomotor assessment was done, the minimum levels Bruce and Bach[4] found sufficient to impair psychomotor performance in the laboratory setting.

Psychomotor Performance

The computation of separate scores for the dominant and nondominant hands on the Finger Tapping and Grooved Pegboard Tests, and the use of two Pursuit Rotor speeds resulted in the production of six scores for each subject at each period of assessment. The group mean scores and standard deviations are shown in Table 2.

These data were analyzed using a repeated measures multivariant analysis of variance procedure. Since the performance levels of the two groups proved to be significantly and inconsistently disparate at baseline, an initial analysis in which absolute score values were employed was repeated using change-scores. These latter scores were derived by subtracting baseline values from subsequent scores so that change

TABLE 2

Scores (means ± SD) of Experimental (E) and Control (C) Subjects on Each Task at Each Assessment Period

Test	Group	Baseline	2 weeks	4 weeks
Finger Tapping				
Dominant hand	E	51.90 ± 5.13	52.04 ± 8.61	54.36 ± 5.11
	C	53.84 ± 9.01	54.67 ± 5.95	55.59 ± 7.41
Nondominant hand	E	47.12 ± 5.31	47.83 ± 6.29	47.84 ± 6.71
	C	48.90 ± 7.02	50.98 ± 6.65	50.42 ± 7.49
Grooved Pegboard				
Dominant hand	E	50.56 ± 4.64	48.00 ± 3.91	47.39 ± 3.70
	C	52.28 ± 4.30	49.17 ± 3.65	48.50 ± 4.36
Nondominant hand	E	52.83 ± 4.73	51.11 ± 3.34	49.56 ± 3.03
	C	56.78 ± 6.36	54.38 ± 5.18	52.22 ± 4.56
Pursuit Rotor				
Slow speed	E	12.16 ± 3.77	13.87 ± 2.59	15.31 ± 2.81
	C	10.44 ± 3.37	13.68 ± 2.35	15.48 ± 2.94
Fast speed	E	5.74 ± 2.59	9.02 ± 2.40	10.15 ± 2.38
	C	5.11 ± 2.84	8.32 ± 2.57	10.45 ± 3.03

in performance rather than absolute level of performance would be represented in the analysis, thereby negating the confounding effect of having the groups starting at different points. As shall be seen, however, the results of these two analyses are similar.

To summarize briefly, the initial analysis in which absolute score values were used indicated that none of the observed performance differences were attributable to trace gas exposure except perhaps those seen in the measures taken from the Pursuit Rotor at its slower speed setting. Reanalysis in which change-scores were used confirmed the negative findings of the initial analysis and further suggested that its one positive finding relevant to Pursuit Rotor performance was in reality an artifact of the groups' differential baseline performance on the task rather than a genuine effect of the experimental condition. The conclusion to be drawn from these two analyses is that exposure to anesthetic trace gases did not adversely affect the psychomotor performance of subjects in the experimental group. The specific details of each analysis and the findings leading to this conclusion are presented below.

Analysis Using Absolute Scores

Three basic comparisons are made in the multivariant analysis that was applied to the present data: the analysis compares the performances of the two groups independent of the time factor (i.e., irrespective of when testing occurred); it compares the performances over time of subjects independent of their group assignment (i.e., irrespective of whether they are experimental or control subjects); and the analysis compares performances based upon the interaction between the factors of group membership and time of assessment. Since the present study concerns possible decrements in the performances of particular subjects (the experimental group) as a function of their having been exposed over time to trace concentrations of anesthetic gases, it is the latter comparison that is of greatest interest. The initial analysis in which absolute score values were used is summarized in Table 3. This analysis revealed the following about the outcome on each task:

Finger Tapping. (1) As is seen in Table 2, group C performed better (i.e., averaged more taps) than group E at all three time periods. In Table 3 we see that group C's superiority is statistically significant and held for both the dominant and nondominant hands ($F = 5.13$, $df = 1$, $p < 0.05$, dominant hand; $F = 11.65$, $df = 1$, $p < 0.01$, nondominant hand). (2) Within groups, no significant changes occurred in performance levels with either hand over time (i.e., no practice effects were observed). (3) No significant interaction effect is observed for either hand between the group and time factors.

TABLE 3

Repeated Measures Multivariant Analysis of Variance Procedure Using Absolute Scores*

Test	Source	Mean squares	*df*	*F*
Finger Tapping				
Dominant hand	Group	100.92	1	5.13†
	Time	43.55	2	2.21
	Group × time	4.34	2	0.22
	Residual	19.67		
Nondominant hand	Group	144.68	1	11.65‡
	Time	12.21	2	0.98
	Group × time	8.78	2	0.71
	Residual	12.41		
Grooved Pegboard				
Dominant hand	Group	57.79	1	9.21‡
	Time	138.12	2	22.01‡
	Group × time	2.85	2	0.45
	Residual	6.27		
Nondominant hand	Group	293.37	1	31.32‡
	Time	138.18	2	14.75‡
	Group × time	3.68	2	0.39
	Residual	9.37		
Pursuit Rotor				
Slow speed	Group	9.07	1	3.52
	Time	153.25	2	59.43‡
	Group × time	9.01	2	3.49‡
	Residual	2.57		
Fast speed	Group	2.85	1	1.09
	Time	220.71	2	84.22‡
	Group × time	2.63	2	1.00
	Residual	2.62		

* *Note*: *Source* refers to the specific comparison being made; i.e., the first comparison is between *groups* irrespective of time, the second is of change over *time* irrespective of group assignment, and the third is of the interaction between group membership and time (*group × time*). The *residual* mean square is a statistical unit representing that portion of the variance in the data not attributable to either of the main factors (group or time) or to their interaction. The residual mean square divided into the mean squares associated with the main factors and their interaction produces the *F* value associated with each comparison. Using the appropriate degrees of freedom (*df*), the level of statistical significance (*p*) associated with each *F* value may be determined from tables found in most standard statistical texts.

† $p < 0.05$.

‡ $p < 0.01$.

Insofar as the Finger Tapping Task is concerned, then, it may be concluded that the two groups differed significantly in their performance levels at the outset, that this disparity was maintained throughout the study, and that no performance decrement attributable to trace gas exposure occurred.

Grooved Pegboard. (1) As is seen in Table 2, group E performed better (i.e., had faster average times) than group C at all three time periods. In Table 3, we see that group E's superiority is statistically significant and held for both the dominant and nondominant hands ($F = 9.21$, $df = 1$, $p < 0.01$, dominant hand; $F = 31.32$, $df = 1$, $p < 0.01$, nondominant hand). (2) Within groups, performance levels significantly improved over time with both hands (i.e., both groups got better with both hands as a function of practice) ($F = 22.01$, $df = 2$, $p < 0.01$, dominant hand; $F = 14.75$, $df = 2$, $p < 0.01$, nondominant hand). (3) No significant interaction effect is observed for either hand between the group and time factors.

Insofar as the Grooved Pegboard Task is concerned, then, it may be concluded that the two groups differed significantly in their performance levels at the outset, that both improved with practice such that their relative positions were maintained throughout the course of the study, and that no performance decrement attributable to exposure to anesthetic gases in trace quantities occurred.

Pursuit Rotor. (1) As is seen in Table 2, group E performed better (i.e., averaged more time-on-target) than group C at the baseline and 2-week assessment periods, but not at the 4-week assessment period. This convergence in performance occurred at both speed settings, and accounts for the statistical nonsignificance of the overall differences between groups reported in Table 3. (2) Within groups, performance levels significantly improved over time at both speed settings (i.e., both groups got significantly better with practice at both speeds) ($F = 59.43$, $df = 2$, $p < 0.01$, slow speed; $F = 84.22$, $df = 2$, $p < 0.01$, fast speed). (3) At the slower speed setting, a significant interaction effect is observed in Table 3 between the group and time variables; i.e., the change in performance over time is significantly different for the two groups. No significant interaction effect is observed between the group and time factors at the faster speed setting.

Insofar as the Pursuit Rotor Task is concerned, then, it may be concluded that the two groups differed significantly in their performance levels at the outset, that both groups improved with practice but that the degree of improvement was greater for group C than for group E, and that the significant interaction effect between the group and time variables seen at the slower speed setting might mean that exposure to trace gases had some affect upon the experimental subjects' ability to perform on this task by the end of the 4-week period.

Analysis Using Change-Scores

The three basic comparisons made in the initial analysis are again made in the subsequent analysis which used change-scores (i.e., the nature of the two analyses is the same; the difference is in the nature of the data being analyzed). The second analysis is summarized in Table 4. This analysis revealed the following about the outcome on each task once initial baseline differences were negated.

Finger Tapping. The groups did not differ significantly in their performance on the Finger Tapping task.

Grooved Pegboard. The groups did not differ significantly in their performance on the Grooved Pegboard task. The significant period (i.e., time) effect associated with nondominant hand performance which emerges in this analysis involves both the groups; i.e., all subjects improved their nondominant hand performance at a rate that was not symmetrical across time intervals.

Pursuit Rotor. With initial baseline performance differences negated, the significant group-by-time interaction effect previously seen on slower speed Pursuit Rotor disappears. That is, the interaction effect emerging from the initial analysis which suggested a possible trace gas influence on performance now seems clearly attributable to the disparity in the groups' baseline performance. Having begun at a significantly higher level of performance than group C, group E simply did not show the same rate of improvement as that group at the slow-speed setting, and hence the illusory interaction effect. The change scores from baseline to 2 weeks and from baseline to 4 weeks are indeed not equivalent for the two groups, but apparently only because they began at different performance levels. On the faster speed setting of the Pursuit Rotor the two groups show only equivalent practice effects.

Discussion

The anesthetic properties of nitrous oxide and halothane are well established; clearly inhalation of these and similar agents in sufficient concentrations produce progressive psychomotor impairment and eventual loss of consciousness. The issue, then, is not whether these agents can have deleterious effects upon psychomotor functioning, but rather whether

TABLE 4

Repeated Measures Multivariant Analysis of Variance Procedure Using Change Scores*

Test	Source	Mean squares	*df*	*F*
Finger Tapping				
Dominant hand	Group	0.01	1	0.00
	Period	47.05	1	2.71
	Group × period	8.68	1	0.05
	Residual	17.38		
Nondominant hand	Group	48.35	1	3.89
	Period	1.33	1	0.11
	Group × period	1.45	1	0.12
	Residual	12.44		
Grooved Pegboard				
Dominant hand	Group	17.01	1	3.78
	Period	7.35	1	1.63
	Group × period	0.01	1	0.00
	Residual	4.50		
Nondominant hand	Group	17.01	1	1.98
	Period	62.35	1	7.27†
	Group × period	1.68	1	0.20
	Residual	8.57		
Pursuit Rotor				
Slow Speed	Group	52.43	1	32.33‡
	Period	47.21	1	29.11‡
	Group × period	0.55	1	0.34
	Residual	1.62		
Fast Speed	Group	3.76	1	1.78
	Period	49.45	1	23.44‡
	Group × period	4.01	1	1.90
	Residual	2.11		

* *Note.* In the analysis using change-scores, two time *periods*—baseline to 2 weeks and baseline to 4 weeks—constitute a main factor rather than the three individual assessment times represented in the initial analysis. This modification is noted by a change in terminology in the *Source* column of the present table, and by a concomitant reduction in the degrees of freedom. The explanatory note accompanying Table 3 is otherwise applicable here.

† $p < 0.05$.

‡ $p < 0.01$.

they do have such effects upon the ongoing functioning of OR personnel under the circumstances of their normal use. Several studies in recent years have indeed reported that under highly controlled conditions of administration some degree of psychomotor impairment can be produced by even trace levels of these agents, but whether nonregulated exposure to similar levels in the OR leads to similar impairment remains to be demonstrated.

In the present study no significant decrements in psychomotor performance were detected although the average levels of trace concentrations to which subjects were exposed prior to testing exceeded levels that previously reported laboratory studies have found sufficient to produce impairment. Because the atmosphere of the OR was episodically sampled rather than continuously monitored in the present study, however, there is no assurance that the average levels of trace concentrations being reported accurately reflect levels encountered by OR workers on a daily basis. In fact, considering the amount of variance among the samples, the mean values represent levels which themselves were seldom if ever actually present. The point, however, is not whether these subjects uniformly received continuous exposure to a certain average level of anesthetic gas, but whether they experienced conditions as they commonly occur in the natural environment of the OR. Such conditions include episodic exposure to anesthetic gases at levels which, on average, are sufficient to produce psychomotor deficits under circumstances of laboratory administration.

Any or all of the aforementioned dissimilarities between conditions found in an OR and those imposed in a laboratory study may have contributed to attenuation of anesthetic effects in the present instance, and/or perhaps through daily exposure the students also developed some degree of increased tolerance to the presence of low levels of anesthetic gases. Alternatively, it might simply be that the psychomotor effects of trace levels of anesthetic gases, being relatively mild, are rather easily overcome when situational demands warrant increased effort; i.e., ongoing demands of the OR not duplicated in the laboratory setting may activate arousal systems that serve to override and negate trace gas effects that might otherwise be observed. In any event, the data from the present study indicate that routine daily exposure to anesthetic trace gases for a 4-week period in the natural environment of the OR does not result in a significant disruption of psychomotor activity, at least not insofar as that activity is assessed by the type of tasks used in this study.

One might argue the irrefutable possibility, of course, that the experimental subjects in this study indeed experienced some degree of psychomotor impairment, but that it went undetected because of either the timing of assessment or the insufficient sensitivity of the tests used. The highly circumscribed, subtle, and/or ephemeral nature of the psychomotor changes posited to make this possibility viable, however, would seemingly also call into question the practical significance of such effects relevant to performance in the OR. In fact, the magnitude of psychomotor impairment typically produced even in tightly controlled laboratory studies, while lending itself to highly significant statistical results, has for the most part been quite small, and the extent of real risk posed by similarly limited performance decrements even should they be found in the OR is at least debatable. For example, in the 1974 study described by Bruce[6] and colleagues "the most striking decrement in performance produced by exposure to trace amounts of anesthetic . . ." amounted to an overall mean increase of 0.36 of a second in the response latencies of subjects to an audiovisual task which they undertook after breathing a steady flow of air containing 500 ppm of nitrous oxide and 15 ppm of halothane for four consecutive hours. A statistically significant anesthetic effect ($p < 0.005$) was also demonstrated by Bruce and Bach[3] in a similar 1975 study wherein 15 ppm of enflurane replaced halothane in the atmospheric mixture, and response latencies on the same task increased by an overall mean of just 0.09 of a second.

While perhaps situations might be hypothesized where delays measured in some hundredths of a second prove catastrophic, realistically speaking, in the absence of concomitant judgmental errors, motor incoordination, or memory lapses, decrements in simple reaction time of this sort are not apt to be particularly consequential in the daily routine of the OR. Furthermore, in both of these aforementioned studies, the tests were presented in a fixed rather than counterbalanced order, and there is the distinct possibility that even these rather minimal performance decrements were somewhat inflated by the fact that the audiovisual task was invariably the first confronting the subjects following their gas exposure; i.e., the reported data may reflect an interaction between test order and gas exposure rather than a main effect of gas exposure alone.

In brief, then, laboratory studies have demonstrated only that trace levels of anesthetic gases when carefully administered—a loose-fitting breathing mask is blamed by Bruce and Bach[4] for some anomalous results in their 1976 study—may produce measurable though relatively limited decrements in psychomotor performance. Trace levels of anesthetic gases in the open atmosphere of an OR have not been shown to produce comparable decrements, nor has the degree of actual risk posed by the occurrence of such decrements been demonstrated. The foregoing is not meant, however, to dismiss all current concerns regarding the potential hazards posed by anesthetic trace substances present in the open OR atmosphere. As a matter of principle it is desirable that even suspected risk be reduced as much and as soon as possible, though, as a matter of reality, the cost of that risk reduction must always be balanced against the degree of demonstrable risk present. The extent to which trace substances threaten the long-term health and/or short-term functioning of OR personnel, therefore, must be subjected to adequate scientific scrutiny, and additional data relevant to both issues must be derived from methodologically sound investigations before valid conclusions can be drawn.

A recent paper by Bentin, Collins, and Adam[9] represents a significant advance in this direction, showing, as it does, both the requisite sophistication in methodology as well as an ingenious approach to the assessment of a unique aspect of human performance—risk-taking behavior. Only the limited number of subjects employed produced unfortunate instability in their data. While awaiting further study, then, and certainly insofar as the integrity of psychomotor activity alone is considered, it would appear that analogue studies may well be overestimating the amount of threat posed by in vivo trace gases.

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ANESTH ANALG
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Antagonism of Pancuronium and Its Metabolites by Neostigmine in Cats

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BOOIJ, L.H.D.J., MILLER, R. D., JONES, M.J.W., AND STANSKI, D. R.: Antagonism of pancuronium and its metabolites by neostigmine in cats. Anesth Analg 58:483–486, 1979.

Antagonism by neostigmine of neuromuscular blockade produced by pancuronium or its metabolites was studied in the cat anterior tibialis muscle-peroneal nerve preparation using constant infusions of muscle relaxants. The ED_{50} of neostigmine (dose which caused a 50% antagonism) was 16, 11, 29, and 26 µg/kg for pancuronium, 3-hydroxypancuronium, 17-hydroxypancuronium, and 3,17-hydroxypancuronium, respectively. Times of onset of neostigmine action were shorter when antagonizing 17-hydroxypancuronium neuromuscular blockade. Duration of neostigmine action when antagonizing 17- or 3,17-hydroxypancuronium blockade was shorter than with pancuronium or 3-hydroxypancuronium. We conclude that more neostigmine is required to antagonize 17- or 3,17-hydroxypancuronium neuromuscular blockade than is required to antagonize pancuronium. Conversely, less neostigmine was required to antagonize 3-hydroxypancuronium blockade.

Key Words: NEUROMUSCULAR RELAXANTS: pancuronium; BIOTRANSFORMATION (DRUG): pancuronium.

REVERSAL of a pancuronium neuromuscular blockade is occasionally difficult, particularly after prolonged administration or in patients with renal or hepatic dysfunction.[1, 2] One explanation is that delayed plasma clearance of pancuronium may result in a neuromuscular blockade too intense to be antagonized.[3, 4] Another possibility is that with impaired routes of excretion, metabolites of pancuronium may accumulate and cause a neuromuscular blockade in addition to that produced by pancuronium. As much as 20 to 30% of an injected dose of pancuronium may be metabolized into one of its hydroxylated metabolites.[5] In man, pancuronium was found to be 2, 50, and 52 times as potent as its metabolites, 3-hydroxypancuronium, 17-hydroxypancuronium, and 3,17-hydroxypancuronium.[6] In this study, we determined the ability of neostigmine to antagonize the neuromuscular blockade produced by the hydroxylated metabolites of pancuronium.

Methods

Twenty-seven cats were anesthetized with chloralose, 250 mg/kg, and urethane, 60 mg/kg, intraperitoneally. Ventilation was controlled thereafter via a tracheostomy. Both external jugular veins were cannulated for administration of drugs. Arterial blood pressure was recorded from a cannula in the carotid artery. The tibialis anterior muscle tendon was freed, sectioned near its point of attachment and attached to a Grass FT10 force displacement transducer. A stimulating, shielded platinum bipolar electrode was placed on the sciatic nerve after it had been sectioned near its point of attachment. Supramaximal stimuli were delivered at a rate of 0.15 Hz and 0.2 msec duration. The resultant twitch contraction was recorded on a polygraph. Temperature was maintained between 36.5 and 37.5 C. After an intravenous bolus of pancuronium or one of its metabolites, a continuous infusion with the same compound was started at a rate adequate to maintain 90% depression of twitch tension. When depression of twitch tension and rate of infusion were constant for at least 20 minutes, a bolus of neostigmine, 5, 10, 20, 30, 50, or 70 µg/kg was administered intravenously, while the infusion of relaxant continued. The 70-µg/kg dose was studied only when reversing a 17-hydroxypancuronium neuromuscular blockade. Further details of this constant-infusion technique have been described previously.[7] The resultant maximal antagonism of twitch depression was calculated as a percentage of the preexisting 90% twitch depression. We also measured the time from the administration of neostigmine to peak effect (onset time) and to 50% restoration of the muscle relaxant depressed twitch tension (duration of action). Subsequent doses of neostigmine were given after the twitch had returned to and remained stable at 90% depression for at least 1 hour. The doses of neostigmine were given by random selection.

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Linear regression analysis and unpaired t-tests were carried out for part of the statistical analyses. Dose-response curves of neostigmine while antagonizing pancuronium and its metabolites were compared by analysis of covariance and the Sheffe's multiple contrast procedure.[8]

Results

The doses of neostigmine required for antagonism of a pancuronium neuromuscular blockade and for antagonism of its metabolites differed significantly (F = 24.6 $p < 0.001$) (Fig 1). The ED_{50} (dose of neostigmine which caused a 50% antagonism) was 16, 11, 29, and 26 µg/kg for pancuronium, 3-hydroxypancuronium, 17-hydroxypancuronium, and 3,17-hydroxypancuronium, respectively (Fig 1). Analysis of the dose-response curves in Fig 1 indicate that: (1) More neostigmine was required to antagonize a neuromuscular blockade from 17- or 3,17-hydroxypancuronium than was required to antagonize neuromuscular blockade produced by 3-hydroxypancuronium or pancuronium itself ($p < 0.05$). (2) Less neostigmine was required to antagonize a 3-hydroxypancuronium neuromuscular blockade than was required to antagonize a pancuronium block ($p < 0.05$). (3) Neostigmine dose-response curves were the same for 17- and 3,17-hydroxypancuronium ($p > 0.10$). (4) Neostigmine dose-response curves did not deviate from parallelism ($p > 0.10$).

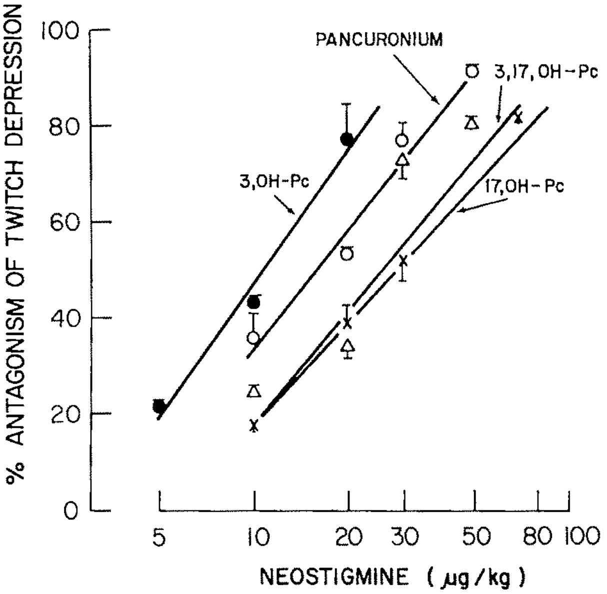

FIG 1. Correlation between dose of neostigmine and percent antagonism of twitch depression induced by pancuronium, 3-hydroxypancuronium (3,OH-Pc), 17-hydroxypancuronium (17,OH-Pc) or 3,17-hydroxypancuronium (3,17,OH-Pc). Lines represent analysis of linear regression. Symbols are means ± SE. See Fig 2 for the number of studies at each dose. With neostigmine, 70 µg/kg, two studies were performed when antagonizing 17,OH-Pc.

The onset times of neostigmine were shortest when antagonizing a 17-hydroxypancuronium blockade ($p < 0.05$) (Fig 2). Duration of action of neostigmine when antagonizing a 17- or 3,17-hydroxypancuronium neuromuscular blockade was less than when pancuronium or 3-hydroxypancuronium were being antagonized ($p < 0.05$) (Fig 2).

Discussion

As much as 20 to 30% of an injected dose of pancuronium is metabolized primarily to 3-hydroxypancuronium and to a lesser extent 17- and 3,17-hydroxypancuronium.[5] Because only 50 to 60% of the administered pancuronium usually is recovered in the urine and bile of most studies,[5, 9, 10] the actual extent to which pancuronium is metabolized may, however, be more than estimated. 3-Hydroxypancuronium is a moderately potent neuromuscular blocking agent. However, even if large amounts of this metabolite were to accumulate after pancuronium, no problem with antagonism should occur since less neostigmine is required to antagonize the neuromuscular blockade

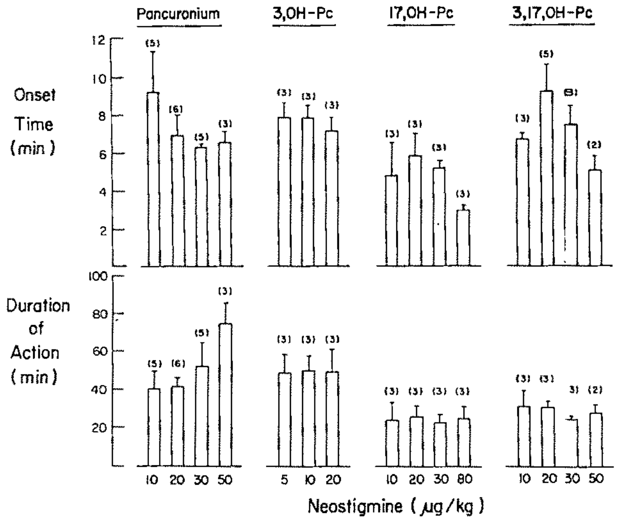

FIG 2. Comparison of onset time (time from neostigmine administration to peak effect) and duration of action (time from neostigmine administration to 50% restoration of the pancuronium depressed twitch tension). Bars represent means ± 1 SE. Values in parentheses represent N.

from this metabolite than from pancuronium itself (Fig 1). Even though more neostigmine is required to antagonize the neuromuscular blockade from the other two metabolites, this should not represent a significant clinical problem since these metabolites are not very potent as neuromuscular blockers[6] and are not present in concentrations as great as those observed with 3-hydroxypancuronium. However, these conclusions should be viewed with some caution. We determined the ability of neostigmine to antagonize the neuromuscular blockade produced by these metabolites when administered singly. With prolonged administration of pancuronium, the neuromuscular blockade probably is a result of the combined effects of pancuronium and all 3 of its metabolites. We assume that since the neuromuscular blockade from pancuronium or one of its metabolites is easily antagonized, a blockade from a mixture of these compounds would also be easily antagonized by neostigmine.

Our present data suggest that muscle relaxants that are not very potent required significantly more neostigmine to antagonize the resultant neuromuscular blockade. For example, 17- and 3,17-hydroxypancuronium are less potent than pancuronium[6] but require more neostigmine for antagonism of their neuromuscular blockade. Similarly, gallamine which is less potent than pancuronium or *d*-tubocurarine also requires more neostigmine for antagonism of its neuromuscular blockade.[11] Not only was more neostigmine required for antagonism of a 17- or 3,17-hydroxypancuronium neuromuscular blockade than that required for pancuronium, but the duration of antagonism was significantly shorter (Fig 2). Perhaps 17- or 3,17-hydroxypancuronium has a greater affinity for the cholinergic receptor at the postjunctional membrane than does pancuronium. Although an attractive hypothesis, binding constants for the metabolites have not been determined. Perhaps these metabolites inhibit acetylcholinerase. This would result in more acetylcholine at the synaptic cleft, requiring more muscle relaxant to compete for the receptor before neuromuscular blockade is produced. This explanation would explain the lesser potency of the 17- or 3,17-hydroxypancuronium metabolite. Also, inhibition of acetylcholinesterase may limit the ability of added neostigmine to further inhibit acetylcholinesterase. Obviously, the ability of these metabolites to inhibit acetylcholinesterase needs to be determined in order to explore this hypothesis further. Lastly, the less potent muscle relaxants obviously require higher plasma concentrations to produce a given level of neuromuscular blockade. Do the increased numbers of muscle relaxant molecules interfere in some way with the kinetics of neostigmine inhibition of acetylcholinesterase? In any event, our observations[11] suggest an inverse relationship between potency of muscle relaxants and amount of neostigmine required for antagonism of neuromuscular blockade. Additional studies are required to confirm the validity and mechanisms of the possible relationship.

In summary, significantly more neostigmine is required to antagonize the neuromuscular blockade produced by 17- and 3,17-hydroxypancuronium metabolites than is required to antagonize the blockade produced by pancuronium or its 3-hydroxypancuronium metabolites. Since the 17- and 3,17-hydroxypancuronium metabolites are not potent as muscle relaxants and apparently do not appear in large amounts, no clinical problems should result insofar as reversal of pancuronium-induced neuromuscular blockade is concerned.

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Paresthesiae or No Paresthesiae?

Does seeking paresthesiae when performing a peripheral nerve block increase the risk of postanesthetic neurologic sequellae? To test this hypothesis the authors prospectively followed two groups of patients who underwent hand surgery with an axillary block. In one group, the axillary plexus was located by actively seeking paresthesiae; in the other group, pulsations of the axillary artery indicated an acceptable position of the injection needle. Mepivacaine, 10 mg/ml, with or without adrenaline, was used. The study included 533 patients, 290 in the "paresthesia group" and 243 in the "artery group." Although unintentional, paresthesiae were elicited in 40% of patients in the "artery group." Postanesthetic nerve lesions were seen in ten patients, eight in the "paresthesia group," and two in the "artery group," all of whom had received mepivacaine with adrenaline. Symptoms varied between light paresthesiae lasting a few weeks, and severe paresthesiae, ache, and paresis lasting more than 1 year. The etiology suspected was needle and perhaps injection trauma to the nerves during blocking. The authors conclude that whenever possible nerve blocks should be performed without searching for paresthesiae. *(Selander D, Edshage S, Wolff T: Paresthesiae or no paresthesiae? Nerve lesions after axillary blocks. Acta Anaesthesiol Scand 23:27–33, 1979)*

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58:487-491, 1979

Hydrogen Ion Concentration versus pH

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UEDA, I., AND EYRING, H.: Hydrogen ion concentration versus pH. Anesth Analg 58:487–491, 1979.

There appears to be a tendency to convert pH values into "hydrogen ion concentrations" using the antilog of negative pH values. The present communication describes the thermodynamic basis of pH to explain that the above procedure is erroneous and that pH values should be treated as primary variables. Acidity expressed by the hydrogen ion concentrations measured by titrations (base excess or base deficit) has no bearing with the "hydrogen ion concentrations" derived by the antilog of negative pH.

Key Words: ACID-BASE EQUILIBRIUM: pH; STATISTICS: mean pH values.

IN ANALYZING acid-base balances, there appears to be a trend to convert pH values into "hydrogen ion concentrations" using the antilog of the negative pH. (The quotation marks are used to denote that the antilog of pH is not equal to the hydrogen ion concentration. Hydrogen ion concentrations are often unmeasurable quantities.) This trend appears to have climaxed in the recent dispute on averaging pH values. Krause[1] and Giesecke[2] suggest that the average of pH should be obtained by first converting the values into "hydrogen ion concentrations" and then converting back to pH. Giesecke[2] argues that "logarithms cannot be averaged until they have been converted back to real numbers."

Recently, Feinstein[3] in an editorial opposed the above argument on the basis of statistical analysis and suggested that the geometric mean of the hydrogen ion concentration may be most representative for the central value, which equals to the arithmetic mean of the direct pH values.

Based on thermodynamics one can support Feinstein's argument that the pH values should be averaged directly rather than using derived "hydrogen ion concentrations." This is because pH is a measure of the chemical potential of the hydrogen ion. It is the chemical potential that usually directly affects biologic systems or chemical reactions, not "concentrations."

From this concept, it is erroneous to claim that deviation from the normal physiologic pH 7.4 value to pH 7.6 is less malignant than shift to pH 7.2 on the ground that the difference in the "hydrogen ion concentrations" between pH 7.4 and 7.6 is 14.7 nM while the difference between pH 7.4 and 7.2 is 23.3 nM. This argument ignores the buffer action and confuses acidities expressed by pH with those expressed by titrated acid content.

The opinion of our group toward averaging pH values has already been expressed.[4] In the present communication, we explain the thermodynamic basis of pH in detail to show the reason why pH values should ordinarily not be converted into hydrogen ion concentrations.

Sørensen first defined pH as the negative logarithm of hydrogen ion concentrations (see, for example, Astrup et al[5]). Presently the pH is defined as a negative logarithm of hydrogen ion activity, a_{H^+}. The hydrogen

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ion activity is related to the concentration through activity coefficient, γ. The uncertainty of γ values is well known and their values are rarely unity. Therefore, the hydrogen ion concentration cannot be estimated from the hydrogen ion activity alone. But that is only a minor part of the present discussion. The definition still gives an impression that the pH scale is used for the convenience of handling a "real number" that has too many digits. The following discussion clarifies the fact that pH is in logarithmic scale not by convenience but by necessity.

Gibbs Free Energy

Biologic reactions usually occur at constant temperature and pressure. The Gibbs free energy, G, is the special function for this condition defined as:

$$G = U - TS + PV \tag{1}$$

where U is internal energy, T is absolute temperature, S is entropy, P is pressure and V is volume.

Any chemical or biologic reaction occurs in the direction such that the Gibbs free energy decreases ($\Delta G < 0$). *The reaction only proceeds spontaneously from a higher state of the Gibbs free energy to a lower state.* In this context, the Gibbs free energy is considered as a "thermodynamic potential."

Chemical Potential

In an ideal solution, the change of the Gibbs free energy of a component i is the chemical potential, μ, of that component (see Appendix 1).

$$\mu_i = \mu_i^0 + RT \ln x_i \tag{2}$$

where x_i is the mole fraction of the i-th component, R is the gas constant and μ_i^0 is the chemical potential of the i-th component when $x_i = 1$, i.e., at the pure standard state.

To apply the above equation to real solutions, activity, a, is used in place of mole fraction. For the hydrogen ion activity, a_{H^+}, the chemical potential is:

$$\begin{aligned}\mu_{H^+} &= \mu_{H^+}^0 + RT \ln a_{H^+} \\ &= \mu_{H^+}^0 + 2.3\ RT \log a_{H^+}\end{aligned}$$

where $\mu_{H^+}^0$ is the chemical potential of the standard state of hydrogen ion and is designated to be zero. Therefore,

$$\mu_{H^+} = 2.3\ RT \log a_{H^+} \tag{3}$$

Biologic activities are linearly related to the chemical potential and, therefore, logarithmically related to the activity of the hydrogen ion, and by definition to pH. Also, *the chemical potential is the only measurable quantity in this equation.*

Nernst Equation

Since pH is a part of chemical potential and is measured by the electromotive force, the understanding of pH calls for knowledge of the electrochemistry of batteries. The Nernst equation describes the relation between the electrical potential, E, and the activity of the components in the chemical reaction at equilibrium.

Consider a chemical reaction where m moles of component A and n moles of component B react to produce m' moles of component C and n' moles of component D.

$$mA + nB = m'C + n'D \tag{4}$$

The electrical potential, E, of the above reaction in equilibrium is given by the following equation (see Appendix 2) which is usually referred to as the Nernst equation:

$$E = E^0 - \frac{RT}{|z|F} \ln \frac{a_C^{m'} \cdot a_D^{n'}}{a_A^{m} \cdot a_B^{n}} \tag{5}$$

where E^0 is the electrical potential of the standard state, z is the valence of the ion, F is Faraday's constant, and a represents the activity of each component.

The Nernst equation is particularly important in the present context when one considers the electrochemistry of the hydrogen ion activity which is measured by a suitable electrode. The principle of the measurement of pH is discussed in the next section.

Hydrogen Electrode

When a metal, M, comes in contact with a solution containing the ion of the metal, M^+, an electrical potential is created by the exchange of electrons, e. The electrode junction is expressed by a vertical bar, $M|M^+$, and the reaction is written as:

$$M|M^+ \quad M = M^+ + e$$

A similar phenomenon is observed when nonmetallic molecules such as hydrogen gas, chlorine gas, etc are exposed to a platinum surface immersed in a solution containing the ion of the same species. For hydrogen gas,

$$Pt|\tfrac{1}{2}H_2|H^+ \quad \tfrac{1}{2}H_2 = H^+ + e$$

Consider a battery cell consisting of

$$Pt(H_2)|HCl|AgCl|Ag$$

which does not contain liquid junctions. The electrode reactions are:

$$\tfrac{1}{2}H_2 = H^+ + e \quad \text{and} \quad AgCl + e = Ag + Cl^-$$

From the Nernst equation

$$E = E^0 - \frac{RT}{F}\ln\frac{a_{Ag}a_{H^+}a_{Cl^-}}{a_{AgCl}a_{H_2}^{1/2}} \tag{6}$$

Because the activities of the solids and the gases at one atmosphere are defined as unity, a_{Ag}, a_{AgCl}, and $a_{H_2}^{1/2}$ vanish in the above equation and

$$E = E^0 - \frac{RT}{F}\ln a_{H^+}a_{Cl^-} \tag{7}$$

For the hydrogen electrode half cell, the Nernst equation becomes

$$E_{H^+} = E^0_{H^+} - \frac{RT}{F}\ln a_{H^+} \tag{8}$$

$E^0_{H^+}$ is used as a reference standard and is defined as zero, therefore,

$$E_{H^+} = -\frac{RT}{F}\ln a_{H^+} \tag{9}$$

According to the definition of pH, the above equation becomes

$$E_{H^+} = 2.3\frac{RT}{F}\text{pH} \tag{10}$$

Because the electromotive force of a half cell cannot be measured, AgCl|Ag or $HgCl_2$|Hg electrodes are usually combined to complete the circuit. Also, a hydrogen electrode is replaced by a glass electrode due to the difficulty of handling a gas. At 37 C, 2.3 RT/F becomes 0.0616 V. Therefore, E_{H^+} becomes 61.6 mV per one pH unit, and pH units are equally spaced on the electrochemical potential.

It is sometimes a matter of concern[6] that the pH is a dimensionless quantity as it is. *It is dimensionless because unit activity is taken as the standard state, and the overall expression for* μ_{H^+} *has the correct dimensions of energy because it contains the factor for energy, RT.*

Effect of pH on Biologic Systems

The linear relationship between chemical potential and biologic activity can be easily demonstrated by the effect of pH upon enzyme activities. As an example, the intensity of firefly bioluminescence as a function of the pH of the solution is shown in Fig 1. An almost symmetrical decrease of the light intensity from the maximal intensity at the optimal pH can be seen on the pH scale. Another example is a partially purified cyclic adenosine-3′,5′-monophosphate phosphodiesterase activity. Again, the enzyme activity decreases almost symmetrically on both sides of the optimal pH activity (Fig 2).

Comment

It appears that the dispute about pH is caused by confusing pH, hydrogen ion concentration and titrated acid content. The concentrations of hydrogen ion or hydroxyl ion required to titrate a solution to neutral or to a certain pH have no bearing on the "hydrogen ion concentrations" derived by taking the antilog of the negative pH value.

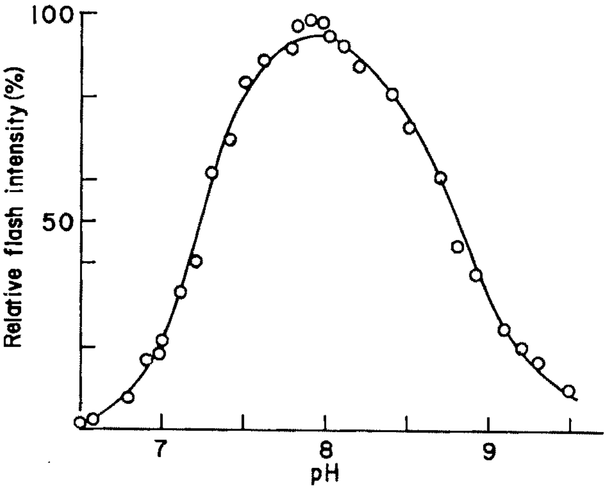

FIG 1. pH-dependency of the intensity of the ATP-induced bioluminescence of solubilized luciferin-luciferase system. The methods of the enzyme preparation and measurement of the light intensity have been reported previously.[4] Symmetrical drop-out of the light intensity occurs on both sides of the maximal intensity at the optimal pH.

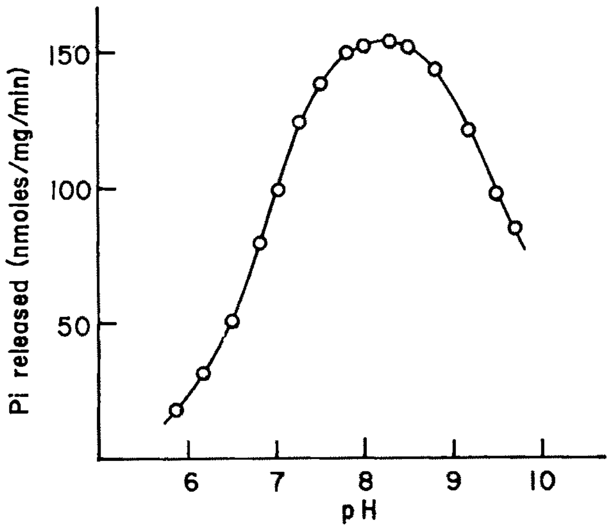

FIG 2. pH-dependency of the activity of partially purified cyclic adenosine 3′,5′-monophosphate phosphodiesterase. The enzyme activity is expressed by the amount of inorganic phosphate liberated from AMP by snake venom nucleotidase after cleavage of 3′-bond by the enzyme. The methods of preparation of the enzyme and the assay of its activity have been reported previously.[5] The enzyme activity decreases symmetrically on both sides of the optimal pH.

For a conceptual model, one can visualize that hydrogen ions exist in active and in inactive forms. It is probably easy to imagine that a biologic fluid such as blood contains more hydrogen ion than pure water at the same pH. The chemical potentials of the two, however, are equal, thus they show the same pH. Suppose two pH values are higher than 7.4 by the same amount. When they are titrated with a strong acid, the amount of hydrogen ion required to reach pH 7.4 is much greater in blood than in water. In the blood acid-base chemistry this quantity is called base excess. When the pH is lower than 7.4 and titrated with a strong base, the amount of hydroxyl ion required to reach 7.4 is again much greater in blood than in water. This quantity is known as base deficit or negative base excess. If the pH alone could provide information on the total available hydrogen ion concentrations, the base excess concept would not be needed. In order to discuss the hydrogen ion concentrations meaningfully, titration is necessary to express this quantity, which is fortunately not on the logarithmic scale.

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APPENDIX 1

Designate the number of moles of each component in an ideal solution by $n_1, n_2 \ldots, n_i$. The volume and internal energy of 1 mole of each component are expressed by $v_1^0, v_2^0, \ldots, v_i^0$ and $u_1^0, u_2^0, \ldots, u_i^0$, respectively. At constant temperature and pressure, the volume, V, and the internal energy, U, of the solution are given as:

$$V = n_1 v_1^0 + n_2 v_2^0 + \ldots + n_i v_i^0 = \Sigma n_i v_i^0 \qquad (11)$$

$$U = n_1 v_1^0 + n_2 v_2^0 + \ldots + n_i v_i^0 = \Sigma n_i v_i^0 \qquad (12)$$

The entropy of 1 mole of each component is expressed by $s_1^0, s_2^0, \ldots, s_i^0$ and designating x_i for the mole fraction of the i-th component, we obtain the entropy of the solution, S, as in the case of an ideal gas mixture

$$S = \Sigma n_i s_i^0 - R\Sigma \ln x_i \qquad (13)$$

where R is the gas constant. When the Gibbs free energy of 1 mole of each component is expressed by $g_1^0, g_2^0, \ldots, g_i^0$, then the free energy of the solution, G, is written from equations 1 and 11 to 13 as

$$G = \Sigma n_i g_i^0 + RT\Sigma n_i \ln x_i \qquad (14)$$

Therefore, the chemical potential of the i-th component in an ideal solution, μ_i, becomes

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right) = \mu_i^0 + RT \ln x_i \qquad (15)$$

The derivation may look complicated because it is performed on an n component system in order to make it general. What this derivation essentially means is that when n components are mixed, forming an ideal solution, internal energy and volume are additive but entropy is not, and carries the excess mixing entropy term $R\Sigma n_i \ln x_i$. Therefore, the total Gibbs free energy consists of summation of internal energy, volume, and entropy plus an excess mixing entropy. It may be stated that the origin of pH in this case is the excess entropy of mixing hydrogen ions.

APPENDIX 2

The free energy change in activities of the reactants in equation 4 at equilibrium is

$$\Delta G = \Delta G^0 + RT \ln \frac{a_C^{m'} \cdot a_D^{n'}}{a_A^{m} \cdot a_B^{n}} \qquad (16)$$

Since $\Delta G = -|z|FE$, where z is the valence, F is Faraday's constant, and E is the electrical potential, dividing equation 16 by this factor yields equation 5.

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Cardiopulmonary Bypass for Tracheal Resection

Partial cardiopulmonary bypass, from femoral vein to femoral artery, was initiated using local anesthesia in two patients undergoing tracheal resection. One patient had a tracheal stricture, with an orificial diameter of 2 to 3 mm, located 3 cm below the thoracic inlet. The second patient had a large intratracheal carcinoid adenoma, located at the level of the thoracic inlet. Following initiation of partial cardiopulmonary bypass in the awake patients, anesthesia was induced and maintained with intravenous agents. Oxygenation was well maintained during the procedures. At the conclusion of surgery endotracheal tubes were inserted and bypass was terminated. The technique offers an alternative in selected situations where access to the airway is difficult or impossible. *(Brickler DL, Parker TM, Dalton ML Jr: Cardiopumonary bypass in anesthetic management of resection: its use for severe tracheal stenosis. Arch Surg 114:847–849, 1979)*

Cost-Effectiveness of Preoperative Electrocardiography

In 812 patients who underwent routine preoperative electrocardiography a mean of 24.6 months after undergoing electrocardiography at the same institution, the frequency of new abnormalities was estimated to evaluate the cost-effectiveness of this procedure prior to an operation. New abnormalities were judged to be either relevant or irrelevant to the assessment of operative risk, depending upon their previously demonstrated correlation with operative and postoperative morbidity and mortality. Since new abnormalities, especially new relevant abnormalities, were found to be relatively infrequent, the cost-effectiveness of routine preoperative electrocardiography was considered to be low. The evidence suggests that when a previous tracing exists, preoperative electrocardiography is most clearly indicated for patients who are 60 years of age or older or whose previous tracing exhibited abnormalities. However, if this suggested protocol had been in effect, new relevant abnormalities would not have been detected in seven patients. Further research is required to develop more sensitive and specific protocols and to evaluate the role of repeat electrocardiography in clinical decision-making. *(Rabkin SW, Horne JM: Preoperative electrocardiography: its cost-effectiveness in detecting abnormalities when a previous tracing exists. Can Med Assoc J 121:301–306, 1979)*

ANESTH ANALG
58: 492–496, 1979

Intravenous Procaine as a Supplement to General Anesthesia for Carbon Dioxide Laser Resection of Laryngeal Papillomas in Children

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LAWSON, N. W., ROGERS, D., SEIFEN, A., WHITE, A., AND THOMPSON, D.: Intravenous procaine as a supplement to a general anesthesia for carbon dioxide laser resection of laryngeal papillomas in children. Anesth Analg 58:492–496, 1979.

Procaine suppresses the cough reflex, decreases laryngeal irritability, and has general anesthetic properties. For these reasons, 14 pediatric patients undergoing CO_2 laser resection of laryngeal papillomas were studied in which an intravenous infusion of procaine (1 mg/kg/min) was added to N_2O-O_2 halothane/enflurane general anesthesia immediately following endotracheal intubation. These patients were compared to nine patients receiving the same anesthesia without procaine.

The mean age of both groups was 11 years. There was no difference between the groups in duration of anesthesia or surgery. Emergence, however, averaged 15 minutes in study patients compared to 36 minutes in the control group ($p < 0.01$). There was no difference in anesthetic concentrations required to maintain satisfactory operative conditions in the two groups. Muscle relaxants were required intraoperatively in seven control patients but in none of the study patients. The surgeon ranked the operative conditions excellent in all study patients but poor in seven of the nine control patients. Five of the latter required postoperative treatment of laryngeal complications, including reintubation in three. Only one of the study patients had postoperative stridor. No evidence of procaine toxicity was noted in the study patients with total doses ranging from 500–3600 mg. Intravenous procaine is useful in pediatric patients having endoscopic laryngeal operations.

Key Words: ANESTHETICS, Local: procaine; ANESTHESIA, Otolaryngolic; SURGERY, Otolaryngolic.

RECURRENT laryngeal papillomatosis occurs most often in children but affects all age groups. The CO_2 laser, introduced in 1971, is now widely used for surgical excision of these lesions.[1] It allows better preservation of cord function and is associated with minimal postoperative pain and edema,[2] a major consideration in children with small airways. The anesthetic management of these patients remains, however, a vexing problem. The airway is compromised before induction of anesthesia and must be shared with the surgeon working in the narrowest part of the upper airway. The vocal cords must be immobile yet rapid recovery of consciousness and protective reflexes is mandatory.

Manipulation of the larynx elicits some of the more primitive reflexes encountered during anesthesia. Recently, the use of topical and/or the intravenous

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administration of lidocaine has been found effective in obtunding cardiovascular reflexes during laryngeal manipulation including endotracheal intubation.[3,4] Historically, the infusion of intravenous procaine has been described as effective in reducing patient response to prolonged laryngotracheal manipulation during thoracic surgery[5] and has been used for many years as a general anesthetic.[6,7] Although the procaine ester is not effective as a topical anesthetic, its intravenous use may have specific advantages over its amide counterpart, lidocaine. These advantages include shorter duration of action due to rapid hydrolysis by pseudocholinesterase, as well as reduction of respiratory tract secretions and production of bronchodilation.[8,9] We therefore examined the use of a continuous infusion of procaine as an adjuvant to general anesthesia in children undergoing CO_2 laser resection of laryngeal papillomas. The use of procaine in this manner, for this purpose, has not been reported.

Materials and Methods

This study was approved by the Human Research Advisory Board and informed parental consent obtained.

Twenty-three patients consecutively admitted for elective CO_2 laser resection of laryngeal papillomas were studied. They were classified as A.S.A. physical status II or III because of the degree of upper airway obstruction but were otherwise healthy. All patients had a normal dibucaine number. This was determined to exclude patients with abnormal cholinesterase. Each patient was assigned on the basis of alternate admissions to either group A (control) or group B (study). Patients in group A received N_2O-O_2 (50:50) and either halothane or enflurane for maintenance of anesthesia during laryngeal manipulation. The choice of halothane or enflurane was made on the basis of previous exposure to these anesthetics. The anesthetic management of patients in group B was the same as that of patients in group A except the former received, in addition, a continuous intravenous infusion of procaine (1 mg/kg/min as a 2% solution in 5% dextrose in water) starting immediately after endotracheal intubation. The dosage was held constant in each patient by the use of a Harvard infusion pump.

Premedication consisted only of an appropriate intramuscular dose of glycopyrrolate (0.002 mg/lb) 1 hour before surgery as an antisialagogue. Anesthesia was induced in both groups by mask using N_2O-O_2 and either halothane or enflurane. Endotracheal intubation was facilitated by the single intravenous injection of succinylcholine (1 mg/kg). Uncuffed endotracheal tubes were used with the lower one fourth covered with adhesive reflective foil to prevent laser burns to the tube. Additional burn protection and airway seal was afforded by placing saline-soaked cottonoids subglottically. Respiration was controlled during surgery. Operating conditions were evaluated independently by the surgeon using a point score system (Table 1). The surgeon was not aware of when procaine was used.

Pulse rate, ECG (lead II), blood pressure, and rectal temperature were monitored continuously. Muscle relaxation was evaluated using a peripheral nerve stimulator. The following data were recorded for comparisons between group A (nonprocaine) and group B (procaine): (1) time from start of anesthesia until satisfactory operating conditions were present; (2) anesthesia and operating times; (3) time for emergence from anesthesia defined as the time between discontinuation of inhalation anesthesia and procaine and the time the patient became fully responsive to command; (4) the concentration of anesthetics needed during maintenance; (5) doses of muscle relaxants, if needed; and (6) total dose of intravenous procaine administered to patients in group B. Postoperative complications were noted in both groups. Student's *t*-test was used for statistical analysis of data.

Results

Nine patients were in group A, 14 in group B. There was no significant difference in age or weight between the two groups (Table 2). Satisfactory operative conditions were achieved, however, in patients receiving procaine so much more easily compared to control

TABLE 1
Surgeon's Scoring System

1—Excellent	Relaxed, no coughing or bucking
2—Good	Relaxed, coughed at start of laryngoscopy only
3—Fair	Poor relaxation, occasional cough during procedure
4—Poor	Poor relaxation, coughing difficult to control

TABLE 2
Patient Data

Group	n	Age (mean ± SE)	Age range	Weight (mean ± SE)	Weight range
		yr	*yr*	*kg*	*kg*
A	9	10.7 ± 1.1	2–34	35.2 ± 3.1	12–82
B	14	11.7 ± 0.5	4–29	34.2 ± 1.3	16–68

patients that the protocol was broken toward the end of the study; the last five patients all received procaine.

There was no significant difference in concentrations of inspired anesthetics for maintenance of anesthesia between the two groups (Table 3). However, seven of the nine patients in group A required muscle relaxants to produce stable operating conditions whereas no patient in group B required relaxants (Table 3).

Anesthesia time was divided into three periods: induction time, operating time, and emergence time (Figure). The mean anesthesia time in group A was 126 minutes compared to 98 minutes in group B. Induction time averaged 26 and 20 minutes in groups A and B, respectively. Operating time averaged 66 minutes in group A, 63 minutes in group B. There was no statistically significant difference between the two groups in these time periods. In contrast, emergence time (Figure) of the two groups was significantly different ($p < 0.01$). Emergence time for patients in group A was 36 minutes compared to 15 minutes for patients in group B. The surgeon rated operating conditions as good or excellent in all 14 patients in group B (Table 3). In only two of the nine patients in group A were operating conditions considered good to excellent. Operating conditions were rated poor in the remaining patients.

TABLE 3

Comparisons of Anesthesia Time Periods*

Patient No.	Highest inspired concentrated gas	Additional neuromuscular blockage	Total procaine dose	Surgeon's score	Complications
	%		*mg*		
Group A†					
1	H 0.75	Yes	None	Poor	Yes
2	H 1.0	No	None	Good	No
3	H 1.25	Yes	None	Poor	Yes
4	H 1.5	Yes	None	Poor	No
5	H 1.5	No	None	Exc.	No
6	E 2.0	Yes	None	Poor	Yes
7	E 2.0	Yes	None	Poor	Yes
8	E 2.5	Yes	None	Poor	Yes
9	E 3.0	Yes	None	Poor	No
Group B‡					
1	H 1.5	No	500	Exc.	No
2	H 0.5	No	2,000	Exc.	No
3	H 1.0	No	1,300	Exc.	No
4	H 0.75	No	1,600	Good	No
5	H 1.0	No	1,600	Exc.	No
6	H 1.5	No	900	Exc.	No
7	H 0.5	No	1,150	Good	No
8	H 1.0	No	3,600	Exc.	No
9	E 3.0	No	1,750	Good	Yes
10	E 2.0	No	3,600	Exc.	No
11	E 2.0	No	2,600	Exc.	No
12	E 2.0	No	2,000	Exc.	No
13	E 2.0	No	600	Good	No
14	E 2.0	No	2,300	Exc.	No

* Abbreviations used are: H, halothane; E, enflurane; Exc., excellent.

† In group A for five patients given halothane, mean 1.20 ± 0.146 SE; for four patients given enflurane, mean 2.36 ± 0.239 SE.

‡ In group B for eight patients given halothane, mean 0.96 ± 0.137 SE; for six patients given enflurane, mean 2.17 ± 0.166 SE.

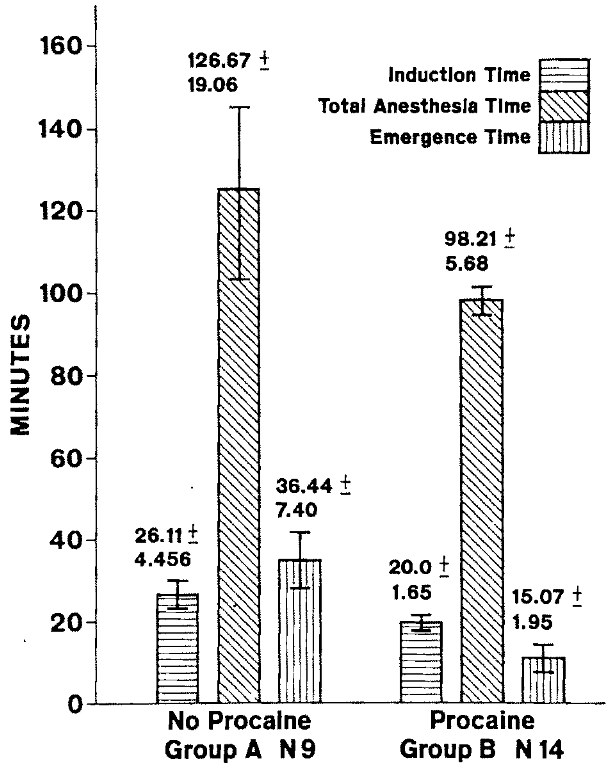

FIGURE. Three periods of anesthesia time: induction, total anesthesia, and emergence.

Complications were noted in five of the seven patients who did not receive procaine and in whom operative conditions were rated as poor (Table 3). The complications included multiple episodes of laryngospasm during emergence and/or postoperative stridor and respiratory distress. Two of the five patients in group A with complications responded to racemic epinephrine; three required reintubation. Only one patient in group B had postoperative respiratory distress sufficient to warrant treatment with racemic epinephrine.

Vital signs remained stable throughout the course of anesthesia in both groups. The total dose of procaine administered ranged from 500–3600 mg (Table 3). No cardiac toxicity was noted on the ECG as evidenced by bradycardia or QRS widening. No symptoms of central nervous system toxicity were noted such as mydriasis, eyelid twitching, or seizures. There was no evidence of neuromuscular blockade in patients who received procaine despite good muscle relaxation.

Discussion

A preliminary study in dogs[10] and clinical reports by others[11] suggested that an intravenous procaine infusion rate of 1 mg/kg/min might be a useful adjunct to surgical anesthesia for obtunding laryngeal reflexes. CNS toxicity is always of concern when using local anesthetics for regional blocks or as a supplement to general anesthesia. However, local anesthetics are known to produce paradoxical, dose-related, biphasic effects on the CNS.[12] Low doses produce analgesia, sedation, and anticonvulsant activity whereas high doses are associated with increased CNS irritability which may progress to convulsions. Seizure activity has not been observed in dogs[10] until the dose of intravenous procaine exceeded 10 times that which produced anesthesia. Thus, we felt that 1 mg/kg/min of intravenous procaine represented the dose which would produce anesthesia without producing toxic CNS effects. These data could, we believed, be transposed to our patients with an additional safety factor in view of the fact that hydrolysis of procaine by serum cholinesterase is more rapid in humans than dogs.[13] Half of the detoxification of procaine in dogs occurs in the liver whereas in humans essentially all biotransformation of procaine takes place in the serum.[14]

Plasma procaine levels were not measured during the present study. Seifen et al,[15] using a recently developed plasma procaine assay,[16] found in anesthetized humans that steady-state plasma procaine concentrations are attained with constant intravenous infusion rates of either 1 or 1.5 mg/kg/min. Plasma procaine levels at an infusion rate of 1 mg/kg/min averaged 12 μg/ml, well below the convulsive range of 20–80 μg/ml.[17] The elimination half-life was found by Seifen et al, to be 7 minutes at all plasma levels and no toxicity was observed in their study with total procaine doses that exceeded 7 g during a 1-hour infusion. Thus the brief duration of action of intravenous procaine requires that it be administered as a continuous infusion to be effective but at the same time the brief duration of action confers a margin of safety should signs of toxicity occur.

Katz and Gissen[18] showed that procaine produces respiratory depression and even apnea in doses that do not affect neuromuscular transmission or produce convulsions. This is ascribed to a generalized CNS depression that was apparent in our patients. The addition of intravenous procaine to conventional endotracheal anesthesia produced excellent operating conditions for intralaryngeal surgery without deep levels of anesthesia or use of muscle relaxants. None of the patients receiving procaine reacted to laryngeal manipulation whereas seven of nine control patients required muscle relaxants at the same inspired anesthetic concentration given to study patients. Indeed, although twitch response remained unaffected in study patients following intubation, the surgeon described relaxation as excellent. This quiescent state, interpreted by the surgeon as muscular relaxation, was most likely a manifestation of the CNS depressant effects of procaine acting in conjunction with the general anesthetic. The effects of intravenous procaine were readily reversible; procaine did not prolong emergence from anesthesia, nor did it produce evidence of CNS toxicity even with doses of as much as 3 g.

The reason for the significantly longer emergence time in control patients remains unclear. There was no statistically significant difference in total anesthesia time or in inspired anesthetic concentrations, even though mean total anesthesia time in control patients was 28 minutes longer than in study patients. Perhaps the longer exposure to inhalation anesthetics, though statistically not significant, contributed to the longer recovery times observed in patients who did not receive intravenous procaine.

Comparison of study and control patients revealed further benefits of the use of procaine as an adjunct to the anesthetic management of children with laryngeal papillomas. The necessity of reversal of residual neuromuscular depression was avoided. Neostigmine contributed directly to airway complications in three of the control patients. Copious secretions developed in response to neostigmine despite pretreatment with glycopyrrolate. Multiple episodes of laryngospasm followed extubation as a result of stimulation of a sensitive, surgically denuded glottis.

The topical use of local anesthetics as an alternative to muscle relaxants and deep anesthesia is rarely effective in these patients having removal of laryngeal papillomas because so much of the anesthetic is usually deposited on the laryngeal growths that are to be removed. Topically applied local anesthetics, furthermore, may leave the glottic opening unprotected from aspiration during emergence from anesthesia. Superior laryngeal nerve blocks are effective in managing adults having surgical excision of laryngeal papillomas but are anatomically difficult to perform in children and may intensify respiratory embarrassment seen if the child becomes excited. Intravenous narcotic supplementation of general anesthesia has been used successfully but has the potential disadvantage of contributing to poor operating conditions by increasing muscle tone.[19] Our experience indicates that when administered in low doses, doses associated with surgical relaxation and reduction of anesthetic requirement,[20] the addition of procaine to the anesthetic management of children undergoing intralaryngeal surgery provides good operating conditions with rapid return of consciousness and protective reflexes. As a result, the incidence of postoperative upper airway problems is significantly decreased.

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Pancuronium Reduces Halothane Requirement in Man

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FORBES, A. R., COHEN, N. H., AND EGER, E. I., II: Pancuronium reduces halothane requirement in man. Anesth Analg 58:497–499, 1979.

We studied the contribution of pancuronium to anesthetic requirement in man by comparing MAC for halothane alone in 18 patients, with that after intravenous administration of pancuronium, 0.1 mg/kg, in 17 patients. In each group, movement was observed in limbs isolated from the circulation by tourniquet. In patients receiving pancuronium, halothane MAC was 0.55%, whereas the control value was 0.73%. Thus pancuronium reduces halothane MAC by 25%.

Key Words: POTENCY, Anesthetic: halothane MAC; ANESTHETICS, Volatile: halothane; NEUROMUSCULAR RELAXANTS: pancuronium.

SINCE the introduction of muscle relaxants to anesthetic practice, controversy has existed over whether or not they possess anesthetic properties.[1-3] The clinical impression that less anesthetic agent is required in the presence of muscle relaxants is countered by the charge that an inability to move in response to a stimulus masks inadequate anesthesia. To resolve this question we have determined whether the non-depolarizing muscle relaxant, pancuronium, reduces anesthetic requirement in man, as measured by halothane MAC.

Methods

We studied 35 male patients between the ages of 24 and 62 presenting for elective surgery. The study was described to each patient and each gave his consent as a participant. Eighteen patients served as the control group, and 17 received pancuronium. No patient was taking medication that would alter anesthetic requirement, and no premedication was given. Anesthesia was induced with up to 4% halothane in oxygen by mask with spontaneous ventilation. At an appropriate depth of anesthesia the trachea was intubated, and ventilation was controlled thereafter. At this point neuromuscular function was tested by supramaximal tetanic stimulation of the median nerve. Compression of 10 ml of air in a ring syringe by opposition of the thumb allowed us to quantitate muscle contraction, and to observe that contraction was sustained. Pneumatic tourniquets were then inflated on one or both legs to 300 torr and on one arm to 200 torr. In patients given pancuronium only, 0.1 mg/kg of the drug was then administered intravenously in the other arm. The mean dose of pancuronium was 8 mg (±0.3 SE). This bolus technique produces similar serum concentrations of pancuronium in patients of different weights at the time of MAC

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determination.[4] In both groups, end-tidal halothane concentration, measured by an infrared halothane analyzer, was then brought to and held at a predetermined level for at least 15 minutes before surgical incision. A positive response to surgical incision was recognized in both groups as a hand or foot movement initiated distal to the tourniquets. MAC was determined in the standard fashion by increasing or decreasing end-tidal halothane concentration by 0.1% in each subsequent patient as the previous patient moved or did not move.[5] For those patients below 30 years, an age correction factor of 1.11 was applied to the required halothane concentration and for those over 55 a factor of 0.84 was applied in accordance with the data of Gregory et al.[6] After incision, response to tetanic stimulation of the median nerve was repeated. In only one patient was this response diminished. This was due to a faulty tourniquet, and the patient was eliminated from the study. MAC for each group was determined by the quantal analysis technique of Waud[7] in which the logistic function is used as a model for the distribution of the probability of responding as a function of dose or concentration. ED_{50} (or MAC) is then estimated directly for each group, and comparison made by unpaired *t*-test.

Results

The groups were comparable in age, with a mean of 39 ± 3.1 (SEM) years in the control patients and 46 ± 3.4 years in the patients given pancuronium. The tourniquets were inflated for 23.4 ± 3.7 (SEM) minutes in the control patients, which was not different from 23.5 ± 2.7 minutes in the patients given pancuronium. The Figure shows the number of patients responding and not responding to surgical incision in both groups at different halothane concentrations. Halothane MAC in the control patients was 0.73 ± 0.04 SEM percent, whereas halothane MAC in patients given pancuronium was 0.55 ± 0.04%, a statistically significant reduction of 25% ($p < 0.01$).

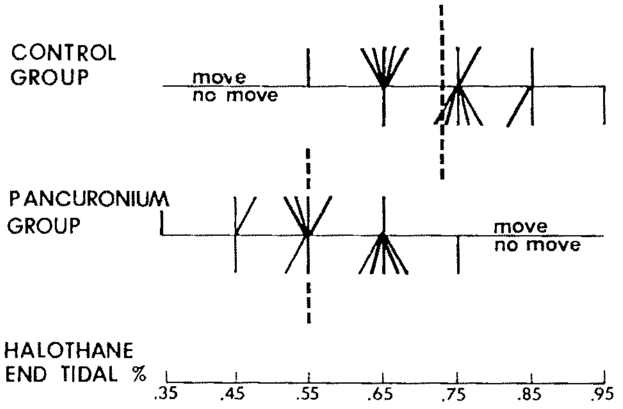

FIGURE. 1: Number of patients moving and not moving in response to skin incision at different end-tidal halothane concentrations is shown. Each line represents one patient. Dotted line indicates the MAC of halothane for each group.

Discussion

This study could be criticized on two counts: (1) the tourniquet interfered with the patient's ability to respond to a noxious stimulus by weakening muscle power or impairing nerve transmission, and (2) pancuronium might leak slowly into the limbs through unoccluded vessels; e.g., in bone. The finding of a MAC for halothane in the normal range in the control patients argues against the first criticism, and a well sustained tetanus after incision in patients given pancuronium counters the second.

Muscle relaxants may reduce anesthetic requirement either through a central or a peripheral action. Animal studies of the central nervous system effects of curare have produced inconsistent results. Pick and Unna[8] showed that although paralyzing doses of curare have no effect on frog brain, doses 2.5 times greater abolish EEG potential. However, frog brain is insensitive to convulsant drugs and very sensitive to depressants in comparison to warm-blooded animals.[8] In cats and rabbits anesthetized with pentobarbital curare produces a cortical stimulation when administered topically to the cortex, or intravenously in a dose of 3 mg/kg.[9] In contrast, intravenous curare in 10 times the paralyzing dose blocks synaptic conduction and abolishes spontaneous cortical activity in the cat.[10] An equivalent dose in the anesthetized dog leads to an increase in cortical electrical activity followed by a diminution.[11]

After intravenous administration of *d*-tubocurarine in man, Matteo et al[12] found concentrations of 4 ng/ml in cerebrospinal fluid within 5 minutes, rising to 15 ng/ml at 1 hour. These are small quantities, yet tubocurarine in small quantities is a potent blocker of neural synapses in experimental preparations.[13] Further support for a central action of non-depolarizing muscle relaxants is the finding that intravenous gallamine or *d*-tubocurarine elevates the seizure threshold to lidocaine in monkeys, whereas decamethonium or succinylcholine does not.[14] This suggests that if pancuronium reduces halothane requirement by a central mechanism, succinylcholine will not do so.

A second possibility is that neuromuscular blockade abolishes muscle spindle afferent input to the reticular activating system (RAS) resulting in deafferentation of the cortex. This theory is supported by the observation that cats paralyzed with gallamine develop electrocortical synchronization patterns identical with those of animals subjected to spinal cord interruption by section or procaine block[15] and is the corollary of the theory that spinal cord afferents, particularly spindle activity, are responsible for wakefulness.[16] A reduction in RAS activity as the sole cause of anesthesia is unlikely,[17] but it could contribute to anesthesia by diminishing cortical input. The ability of subparalytic doses of decamethonium to abolish conditioned reflexes in rats is ascribed to the same mechanism.[18] Further support for the role of the spindle afferents is found in the EEG arousal pattern seen in man after muscle fasciculation in response to succinylcholine or decamethonium.[19] If this explanation is correct, then all muscle relaxants should reduce anesthetic requirement to the same degree in doses that abolish neuromuscular activity.

Clinical data too are conflicting. A series has been reported[1] of three patients "anesthetized" with curare who had no pain or recollection of surgery, and two others given smaller doses who felt pain and remembered. Two of the former were hypovolemic and hypotensive, the third was a 70-year-old woman premedicated with 8 mg of morphine. In surgical patients, full curarization leads to an "alpha-like" rhythm on EEG which cannot be modified by visual stimuli as in the conscious patient. Nor do painful stimuli produce the expected EEG changes in a curarized patient.[20] A subjective account has been provided by Smith,[2] who although reporting normal sensation and response to pain after receiving a paralyzing dose of curare, felt "drowsy" at the end of the experiment. These studies all sought to establish whether or not curare by itself produced anesthesia or analgesia, rather than whether it modified anesthetic requirements.

Muscle relaxation with pancuronium should be viewed as an adjunct to general anesthesia which not only provides paralysis but also decreases anesthetic requirement. However, the implication of our findings is not that a patient paralyzed is a patient anesthetized. We agree with Cullen[3] that muscle relaxation alone is no substitute for adequate anesthesia.

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ANESTH ANALG
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Impairment of Tracheal Ring Ciliary Activity by Halothane

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MANAWADU, B. R., MOSTOW, S. R., AND LAFORCE, F. M.: Impairment of tracheal ring ciliary activity by halothane. Anesth Analg 58:500–504, 1979.

The effects of varying concentrations of halothane on tracheal ciliary activity were studied using a ferret tracheal organ culture technique. Using 1% and 2% halothane produced no impairment of ciliary activity, while 3% halothane caused some ciliostasis; 4% and 5% halothane produced rapid cessation of ciliary activity. Recovery was prompt and complete after exposure to 4% halothane for as long as 3 days, but after 4 days of exposure recovery was incomplete and after a week of exposure death of ciliary cells occurred.

Key Words: ANESTHETICS: Volatile, halothane; LUNG, Trachea: cilia.

PHYSICAL clearance of inhaled or aspirated bacteria, an important lung defense mechanism, depends upon ciliary activity of the respiratory epithelium. Cilia are composed of microtubules and the integrity of these structures is essential for ciliary activity. Anesthetics are capable of distorting microtubular structures[1–4] and halothane has been shown to reversibly impair ciliary activity.[5] Thus impaired ciliary activity after inhalation anesthesia may be a contributory factor in the development of postoperative pulmonary infection.[6]

Methods used in prior studies to quantitate ciliary activity can be classified as direct or indirect.[7–12] In the indirect methods, the rates of clearance of carbon dyes, radiolabeled particles or mucous flow rates are determined as indices of ciliary activity. A disadvantage of indirect techniques insofar as anesthetics are concerned is that the effect of anesthetics on the physical characteristics of mucus and on the synchrony of ciliary activity are often unknown and difficult to control. With direct techniques cilia are observed either in vivo or in vitro through optical devices. The majority of in vitro studies on respiratory tract cilia have consisted of exposing excised strips of ciliated epithelium to anesthetic vapors. Recently, however, tissue cultures of respiratory epithelium have been prepared by punch biopsies of the tracheal epithelium[12] and ciliary activity estimated on the basis of cinephotomicrographically recorded speed of rotation of clusters of ciliated epithelial cells. A disadvantage of this technique is that the speed of rotation of a cell cluster depends not only upon the ciliary activity but also on the weight of the cell mass, the presence of damaged or nonciliated cells in the cell cluster, viscosity of the immediate environment, and the presence or absence of mucus, all variables that are difficult to control or standardize.

Recently, refinements of tissue culture techniques have resulted in the reintroduction of tracheal organ culture techniques to assess respiratory epithelial activity.[13, 14] These in vitro techniques preserve the integrity of the respiratory epithelium for prolonged periods. This report describes the use of tracheal organ culture systems to investigate the effects of both acute and prolonged exposure to halothane on ciliary activity.

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MATERIALS AND METHODS

Organ Culture

The organ culture technique used in these studies is a modification of the method described by Hoorn and Tyrell.[14] Following an overnight fast, ferrets were given a lethal dose of sodium thiopental intraperitoneally and exsanguinated by cardiac puncture. After everting the skin to provide a sterile fur-free environment over the neck and thorax, the trachea was isolated from the thyroid cartilege to the carina by blunt, bloodless dissection. The trachea was transected and placed in a sterile screw-top tube containing L-15 tissue culture medium[13] which maintains a stable pH and is largely responsible for the prolonged survival of the tissues. Using laminar flow conditions, the excised trachea was transferred to a Petri dish. All adherent connective tissues were carefully dissected and complete rings were prepared by cutting transversely between the tracheal cartileges. The rings were carefully transferred to sterile screw-top tissue culture tubes (Flow Laboratories, Rockville, MD), one ring per tube, containing 1 ml of L-15 medium, to which L-glutamine (1% final concentration), 100 units of penicillin and 20 μg of gentamicin had been added. Tubes were then rolled in a tissue culture rotator at 37 C at eight revolutions per hour. Ciliated epithelium prepared in this fashion regularly survived for periods of 30 to 50 days, and occasionally up to 90 days. To prevent accumulation of debris in the center of the ring, which would obscure the cilia, the tubes were shaken gently each day.

Grading of Ciliary Activity

The screw-top tubes were removed from the tissue rotator and placed in a water bath at 37 C while waiting to be examined. The ciliary activity was graded by determining the percentage of cilia beating on each ring using transmitted light and the 10× objective of an inverted microscope. Although differences in the vigor and speed with which the cilia beat were observed, only the presence or absence of ciliary activity was quantitated in this study. After quick observation of the entire ciliary epithelium of the ring a prominent "landmark" on the epithelium was located. From this point the number of microscopic fields required to scan the entire epithelium was determined. For example, if eight fields were required to scan the entire ring, each field represented 12.5% of the entire epithelium. If all the fields showed ciliary activity, it was scored as 100%. If ciliary activity was absent throughout, the score was zero. However, if only 3½ fields showed ciliary activity the ring was scored as 44%. With experience, the percentage of ciliary activity could be determined rapidly, and in this study all readings were made as unknowns by the same observer (S.R.M.). After preparation of the rings, ciliary activity increased over the first 24 to 72 hours. Also, during this period some cells were shed and the medium was changed daily to remove the cellular debris and excess mucus. Baseline data were not obtained until 72 hours after preparation of the rings.

Exposure to Halothane

A Boyle's anesthetic machine was adapted to vaporize halothane with air. A Dräger vaporizer delivered specified concentrations of halothane. Sterile tubing containing a 2-μ Millipore filter (3M Company) was connected to the gas outlet from the anesthetic machine, and a sterile 19G, 20-cm needle attached to the tubing. The needle and the screw-capped tubes were flamed and the tip of the needle placed below the fluid level of the medium. Gas was bubbled through the medium at a rate of 50 ml/min for 6 minutes. This completely replaced the air in the tube with the predetermined halothane concentration. The tubes were held in a slanted position during the gas bubbling phase, so that the tracheal ring was at the bottom.

The bubbling gently agitated the ring, helping to dislodge mucus and debris adherent to the epithelium. Control tubes were similarly treated with air and no damage from bubbling was noted. The tubes were then stoppered and sealed to ensure an airtight closure. The culture tubes were placed horizontally and rotated in a tissue culture rotator which ensured a gas-liquid interface. Thus the cilia were exposed to the concentration of halothane at which the tubes were filled. This procedure was repeated every 24 hours.

Experimental Design

The percentage of actively beating cilia on each ring was recorded on the day of the experiment and each experiment consisted of four tubes. The allocation of the tubes was such that each experimental group had an equal number of tubes with the high and low percentages of ciliary activity and their mean ciliary percentage was similar. The tubes were flamed, tightly closed, and placed in the tissue culture rotator horizontally, and incubated at 37 C for 2 hours before the ciliary activity was determined. Rotation of the tubes provided a gas-liquid interface which ensured that the cilia were exposed to the predetermined concentrations of halothane.

Groups of tubes were exposed to halothane concentrations of 1.0, 2.0, 3.0, 4.0, and 5.0%, confirmed by aspirating a sample and measuring in a mass spectrometer (Perkin-Elmer). Control tubes were exposed to air, and the percentage of ciliary activity was determined in a blind manner every 24 hours.

A second group of tubes was exposed to 4.0% halothane or room air and sealed; the percentage of ciliary activity was determined every 24 hours. After the 3rd day of exposure to halothane, one set of four tubes was flushed completely free of halothane each day using room air, the medium was changed twice, and recovery of ciliary activity was determined.

Results

Ciliary activity after exposure to increasing concentrations of halothane is summarized in Fig 1. Ciliary activity of the tracheal rings exposed to 1% and 2% halothane showed no impairment, while 3% halothane caused some ciliostasis. Dramatic reductions in the ciliary activity occurred with halothane concentrations of 4% and 5%.

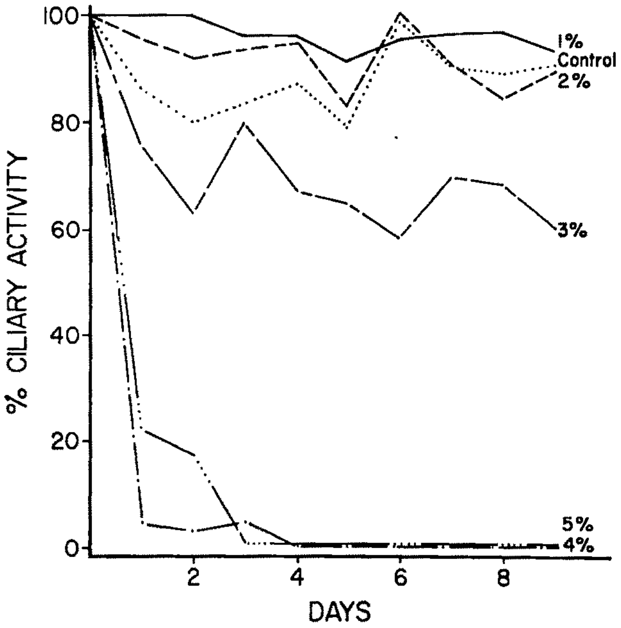

FIG 1. Impairment of ciliary activity with halothane. The ciliated epithelium of ferret trachea was exposed to varying concentrations of halothane and observed for several days.

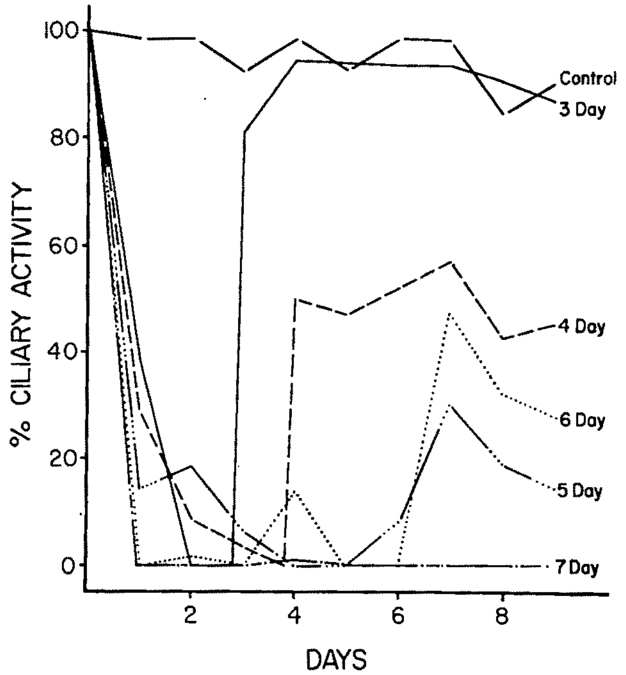

FIG 2. Recovery of halothane-impaired ciliary activity. The ciliated epithelium of ferret trachea was exposed to 4% halothane for periods of 3 to 7 days. Following exposure, the cilia were exposed to room air and observed at 24-hour intervals.

Results of recovery experiments at 4% halothane concentrations are summarized in Fig 2. Tracheal rings could be exposed in 4% halothane for as long as 3 days with complete reversal of ciliostasis after the removal of the anesthetic. After 4 days of exposure, recovery in room air was incomplete, and after 1 week of 4% halothane, death of ciliary cells was noted.

Discussion

Use of organ cultures of tracheal rings to quantitate ciliary activity has advantages over indirect methods and tissue culture methods. With indirect methods the clearance rates of mucus, dyes, carbon or radioactive particles are utilized to estimate ciliary activity.[7-10] The quality and quantity of the mucus influence these clearance rates, and it is difficult to separate the effects of changes due to anesthetically induced alterations in the character of mucus from those attributed to changes in ciliary activity.[5,10] Humidity is a well known factor altering mucus which affects the clearance rate of particles, although the cilia per se remain unaffected. The effects of anesthetics on the production, secretion, quantity, and quality of mucus are unknown. Thus many authors refer to clearance rates as an indication of the mucociliary activity.[7-10] Further, in vivo studies of ciliary activity have shown that ciliated epithelium coordinates its rhythmic activity to form definite pathways along which mucus is cleared.[15] Thus there could be a block in the clearance of particles due to incoordination of ciliary activity. With indirect methods the effects of anesthetics on mucus and ciliary activity coordination are unknown or uncontrolled.

Direct observation of ciliated cells in tissue cultures to estimate ciliary activity overcomes the above objections, but has a disadvantage in that the integrity of the respiratory epithelium is destroyed and uniformity of the cell clusters cannot be controlled.[12] Thus, some cell clusters would consist of nonciliated cells and goblet cells that would influence the speed of rotation of the cell cluster. Use of tissue cultures of respiratory epithelial cells and quantitation of ciliary activity by determining the speed of rotation of the cell clusters has limitations.

The advantages of the organ culture are that the integrity of the respiratory epithelium is maintained and that ciliary activity can be directly observed. The use of L-15 medium consisting of a number of amino acids with different pKa values obviates the need for buffers and for CO_2 gassing of the cultures.[14] Further, use of a tissue culture rotator exposing the tracheal rings to a gas-liquid interface, in contrast to having the rings completely immersed in the tissue culture medium all the time, greatly prolongs the survival of the tissues.[13] The existence of a gas-liquid interface was crucial in our study since the respiratory epithelium could be exposed to anesthetic concentrations merely by replacing the air in the culture tube with a known concentration of the anesthetic agent.

Although there are many different types of cilia throughout nature, they all have a similar electron microscopic structure consisting of nine pairs of peripheral and one pair of central microtubules.[3,4] Halothane disturbs this spatial configuration, causing microtubules to collapse reversibly when exposed to a 1.0 mM concentration of halothane.[16] Halothane also inhibits oxidative phosphorylation, the metabolic source of energy for ciliary beating.[17] Both these factors may contribute to the inhibition of ciliary activity produced by halothane.

Our studies showed that 4% halothane or more was required to impair ciliary activity and that while prolonged exposure is cytotoxic, exposure for less than 4 days is followed by complete recovery of ciliary activity. In previous studies where mucociliary flow was measured by radioactive droplet methods, depression was seen at much lower concentrations (0.6 MAC halothane).[10] A possible explanation for the variance of these results is that clearance rates of radioactive droplets are affected by changes in the character of mucus as well as by changes in ciliary activity and coordination, all of which may be affected by anesthetic agents. In the present study we examined ciliary activity alone. In our model there is a threshold level between 3% and 4% halothane concentration above which the ciliary activity is dramatically depressed.

Since 4% halothane concentrations are rarely used in clinical practice, and then only briefly for induction of anesthesia, we conclude that at the usual concentrations (less than 2% halothane), there is minimal depression of ciliary activity. Since most operations are of less than 6 hours duration, whatever slight depression of ciliary activity might occur with clinically effective concentrations of halothane intraoperatively would be rapidly reversible at the conclusion of anesthesia.

ACKNOWLEDGMENTS

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Erratum

In the paper "Local Anesthetics and Pulmonary Venous Admixture in Pregnant and Nonpregnant Sheep" by Egon Lanz, Bruce Ruiz, and Helene Schlereth (Anesth Analg 58:318–321, 1979) there is an error in the "Discussion." Beginning with the second paragraph, the "Discussion" should read as follows:

With the exception of chloroprocaine, infusion rates used gave blood concentrations of bupivacaine, etidocaine, and lidocaine that have been measured clinically during regional anesthesia.[4] Because of lower cholinesterase activity in sheep, there is a slower chloroprocaine hydrolysis rate in sheep than in man; this factor and the relatively higher dosage of chloroprocaine we administered suggest that the plasma concentrations of chloroprocaine may have been higher in this study than under clinical conditions. Nevertheless, the concentrations were not high enough to elicit signs of central nervous system stimulation or toxicity.

In this study, we observed that clinically measurable plasma concentrations of bupivacaine, etidocaine, lidocaine, and possibly higher concentrations of chloroprocaine did not induce any significant changes of pulmonary venous admixture in sheep. On the other hand, local anesthetics have been reported to have direct effects on the smooth muscles of various vessels that might be dose dependent; in lower concentrations, vessels are constricted and in higher concentrations, dilated.[4, 13, 14] Vasoconstriction of the pulmonary vessels, which might be a direct or indirect effect of local anesthetics, has been described.[15, 16] The latter might result from potentiation of the response of smooth muscle to catecholamines. Also, a direct relaxant effect on bronchial smooth muscle has been reported.[4]

There are several possible explanations for the absence of any effects of local anesthetics on pulmonary venous admixture in our study. Most likely, the effects of local anesthetics on the smooth muscle of pulmonary vessels and airways were not enough to result in any changes of pulmonary venous admixture. Other possibilities are that the local anesthetics changed ventilation and perfusion commensurately so that either the ventilation-to-perfusion ratio remained within the range of preinfusion values or the changes of ventilation and perfusion caused by the anesthetics were offset by compensatory mechanisms altering the ventilation-to-perfusion ratio toward the control values.

The results of this animal study give reassurance to the question of the safety of regional anesthesia. However, similar studies in man comparing the effects of local anesthetics on pulmonary venous admixture to those of general anesthetics would be more relevant to this problem. Such studies would be of special interest to those physicians giving anesthesia to the respiratory-risk patient for whom any untoward effects on pulmonary venous admixture would be undesirable.

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Pulmonary Antibacterial Defense Mechanisms Are Depressed by Halothane

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MANAWADU, B. R., MOSTOW, S. R., AND LAFORCE, F. M.: Pulmonary antibacterial defense mechanisms are depressed by halothane. Anesth Analg 58:505-509, 1979.

Pulmonary antibacterial activity was determined by challenging halothane-exposed and control mice to radiolabeled (^{32}P) *Staphylococcus aureus* produced by an aerosol generator and by determining the relative changes in viable bacterial and radioisotope counts in ground lung immediately after exposure and 4 hours later. Mice that were anesthetized for 4 hours with 1 or 2 MAC halothane and allowed to recover for 1 hour showed higher 4-hour bacterial counts when compared to controls, while radioisotope counts were the same in both groups. These data indicate that 1 and 2 MAC halothane anesthesia is associated with depressed lung bactericidal activity but that physical clearance mechanisms are not depressed.

Key Words: ANESTHETICS, Volatile: halothane; LUNGS: antibacteria defense mechanisms.

PNEUMONIA after general anesthesia is a considerable source of morbidity and occasional mortality. These infections have been attributed to aspiration of gastric contents, use of contaminated equipment, tracheal trauma, defective cough mechanism, retention of sputum, and atelectasis. However, common denominators in most reports have been an increased incidence with age, thoracic surgery, and duration of operation.[1-3] One possible contributing factor, not extensively studied, is anesthesia-related depression of pulmonary antibacterial defenses.

Pulmonary defenses against bacteria largely consist of physical clearance by the mucociliary escalator system and phagocytosis by pulmonary alveolar macrophages (PAM). Studies have shown that many exogenous and endogenous factors may compromise the pulmonary bactericidal activity.[4]

In the most comprehensive experimental study of the effects of general anesthetics on lung bactericidal activity, Goldstein et al[5] have shown that mice had depressed lung bactericidal activity against *Staphylococcus aureus* during anesthesia with methoxyflurane or cyclopropane, whereas halothane anesthesia had no effect. However, halothane is known to markedly depress the extravascular mobilization of neutrophils.[6] Further, cell-mediated cytotoxicity[7] and chemotaxis of neutrophils are impaired by halothane anesthesia.[8] Therefore, we felt it important to restudy the effect of halothane anesthesia on total lung bactericidal activity.

Materials and Methods

Female Swiss-albino mice weighing 15 to 20 g each were used in all the experiments. The animals were housed in plastic cages and fed Purina Lab Chow and water ad libitum.

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Exposure to Halothane

Mice were anesthetized in a special cage[9] into which halothane in humidified air was delivered from a Boyle's anesthesia machine at a flow rate of 6 L/min. The concentration of halothane was checked by mass spectrometry (Perkin-Elmer). Mice were anesthetized with either 1 or 2 minimum alveolar concentrations (MAC) of halothane, according to the experimental protocol as described below. The animals were anesthetized within 5 to 10 minutes. Carbon dioxide accumulation was controlled by placing soda-lime in the bottom tray. Telethermistor probes were placed rectally and temperature monitored continuously. Temperature was maintained at constant levels by heating with an infrared lamp. After 4 hours of anesthesia the animals were allowed to recover in room air for 1 hour before being exposed to the aerosolized bacterial challenge.

Exposure to Bacterial Aerosol

Staphylococcus aureus was grown in phosphate-poor broth with 1 mCi of carrier-free ^{32}P. After 16 hours of growth in a Shaker water bath, the bacteria were harvested by centrifugation and washed twice in normal saline to remove unattached radiolabel. The washed bacteria were then resuspended in 15 ml of saline.

The bacterial aerosol generator and exposure chambers were built at the Instrumentation and Model Facility, University of Vermont, Burlington, VT.[10] Briefly, this plexiform glass tubing system allows the generation of *S. aureus* as droplet nuclei so that most of the inhaled bacteria are deposited in the distal recesses of the lung.

Mice that had recovered from anesthesia and unanesthetized control mice were randomly placed in individual compartments of the cages and exposed to radiolabeled aerosolized *S. aureus* for a period of 30 minutes. Immediately after exposure (0 hour) and 4 hours later, mice were killed by luxation of the neck. The lungs were aseptically removed, homogenized in broth, serially diluted, and plated in triplicate. Plates were incubated at 37 C for 24 to 36 hours and the colonies counted. Radioactivity was assayed by transferring a separate aliquot of the homogenate into scintillating vials containing 1 ml of soluene before being digested overnight and counted in a scintillation spectrometer using a toluene base scintillation fluid. After correction for background, quench, and dilution, the radioactivity was expressed as counts per minute per milliliter of material assayed.[10]

Experimental Design

Each experimental set consisted of 24 mice, divided into four groups of six mice each (A, B, C, and D). Groups A and B were anesthetized for 4 hours. Animals were then allowed to recover and 1 hour later were randomly placed with unanesthetized control mice (groups C and D) in the bacterial aerosol chamber and were exposed to aerosolized *S. aureus* for 30 minutes. Groups A and C (0 hour) were immediately sacrificed; groups B and D were sacrificed 4 hours later.

Four sets of experiments with 24 mice each were used to study the effect of 1 MAC halothane and no mortality was observed. However, about 10% of the mice anesthetized at 2 MAC died, possibly due to respiratory obstruction associated with deeper levels of anesthesia. Thus larger numbers of mice were used in the experimental sets 5, 6, and 7 so as to give a total of 24 mice for each of the groups A, B, C, and D as shown in Table 2.

Calculation of Bactericidal Values

Individual mouse bactericidal values were obtained by using ^{32}P count as an index of the bacteria inhaled initially by the mouse.[10] To calculate the intrapulmonary killing of *S. aureus* the change in the ratio of bacterial count/isotope count from 0 to 4 hours was determined:

$$K_0 = \frac{\text{Bacterial count at 0 hour}}{\text{Isotope count at 0 hour}}$$

$$K_4 = \frac{\text{Bacterial count at 4 hours}}{\text{Isotope count at 4 hours}}$$

A K_0 value was calculated for each individual mouse sacrificed at 0 hour. The percentage of viable bacteria remaining at 4 hours could then be determined for each individual mouse by using the K_0 value calculated from the mice sacrificed at 0 hour:

$$\%\ \text{bacteria remaining at 4 hours} = \frac{K_4}{K_0} \times 100.$$

The advantage of this technique is that it corrects for the physical removal of bacteria, the percent bacteria remaining at 4 hours being a measure of in situ macrophage function.[10, 11]

Calculation of Physical Clearance

The ^{32}P count is an index of the bacteria inhaled and the difference between the isotope counts at zero and 4 hours gives a measure of the bacteria physically cleared from the lungs.

Statistical Analysis

The percentage of bacteria remaining at 4 hours was calculated for the halothane-exposed and control mice. The statistical significance of the difference between these percentages was calculated by Student's *t*-test. The *t*-test was also applied to determine statistical significance between the mean isotope counts at 4 hours in anesthetized and unanesthetized control mice.

Results

One hour after recovery from 1 MAC of halothane, mice that had been anesthetized were behaviorally indistinguishable from unanesthetized control mice. However, some of the mice anesthetized at 2 MAC were still lethargic 1 hour after cessation of halothane anesthesia.

Intrapulmonary bactericidal activity was depressed in both groups 1 and 2 MAC halothane-anesthetized animals (Tables 1 and 2). Mice recovering from 1 MAC halothane anesthesia and then exposed to aerosolized *S. aureus* had 46.1% of the initial bacterial

TABLE 1

Effect of 1 MAC Halothane on Lung Bactericidal Activity*

Set no.	No. of mice	Group	No. of mice in each group	Mean 4-hour bacterial counts	K_0	% bacteria remaining
1	24	D	6	9,888 ± 2,120	8.7	21.8 ± 2.0
		B	6	18,666 ± 1,561	9.0	32.6 ± 1.7
2	24	D	6	9,666 ± 1,268	15.6	29.2 ± 4.7
		B	6	13,888 ± 2,047	17.9	28.7 ± 4.5
3	24	D	6	7,633 ± 810	47.6	19.5 ± 2.3
		B	6	22,433 ± 4,655	44.6	61.5 ± 15.7
4	24	D	6	29,800 ± 4,569	75.2	30.7 ± 4.2
		B	6	72,766 ± 7,719	88.2	52.1 ± 6.3
Totals	96	D	24			
		B	24			
Mean		D		13,041 ± 2,062	9.9 ± 2.0	24.5 ± 2.0†
		B		28,537 ± 4,741	21.0 ± 2.7	46.1 ± 6.5†

* The value K_0 was calculated from mouse groups A (N = 24) and C (N = 24) as described in "Materials and Methods." Values shown are means ± SE. Group D, control mice; group B, mice given halothane.

† $p < 0.005$.

TABLE 2

Effect of 2 MAC Halothane on Lung Bactericidal Activity*

Set no.	No. of mice	Group	No. of mice in each group	Mean 4-hour bacterial counts	K_0	% bacteria remaining
5	22	D	6	9,094 ± 825	23.9	15.5 ± 1.3
		B	4	17,752 ± 1,177	19.8	25.9 ± 2.6
6	46	D	12	11,458 ± 1,856	84.7	20.6 ± 3.5
		B	10	22,288 ± 4,297	79.6	37.0 ± 7.2
7	28	D	6	10,278 ± 1,100	46.9	21.4 ± 2.4
		B	10	20,916 ± 1,626	45.9	47.9 ± 3.2
Totals	96	D	24			
		B	24			
Mean		D		10,129 ± 777	9.7 ± 1.6	19.1 ± 1.5†
		B		20,157 ± 1,157	18.7 ± 2.1	40.1 ± 2.9†

* The value K_0 was calculated from mouse groups A (N = 24) and C (N = 24) as described in "Materials and Methods." Values shown are means ± SE. Group D, control mice; group B, mice given halothane.

† $p < 0.0005$.

inoculum viable at 4 hours, whereas control mice had 24.5% ($p < 0.005$) (Table 1). Mice recovering from anesthesia with 2 MAC halothane also had depressed bactericidal activity with 40.1% of the bacterial inoculum viable compared to 19.1% in the control animals ($p < 0.0005$) (Table 2). Thus, 1 and 2 MAC halothane anesthesia were associated with depressed in situ bactericidal activity against *S. aureus.* At 4 hours the differences in the percentage of viable bacteria in mice exposed to halothane and in control mice were not statistically significant following either 1 MAC ($46.1 - 24.5 = 21.6$) or 2 MAC ($40.1 - 19.1 = 21.0$) halothane anesthesia. Statistical analysis for significance of the viable bacteria between control mice and mice exposed to 1 MAC halothane showed $p < 0.005$. Similar groups exposed to 2 MAC halothane showed a higher degree of significance ($p < 0.0005$).

Physical clearance of bacteria as measured by the change in radiolabel counts at 4 hours showed no significant difference between the anesthetized and control mice (Table 3).

Discussion

Pulmonary alveolar macrophages (PAM) play a key role in the antibacterial defenses of the lung.[12]

Phagocytosis and intracellular killing of bacteria by PAM are oxygen-dependent energy utilizing processes.[13] Halothane is an anesthetic known to depress oxidative phosphorylation.[14] Additionally, the integrity of the microtubular structures of the macrophages which are essential for phagocytosis is distorted by halothane.[6] Theoretically, then, halothane might be expected to depress PAM function. However, Goldstein et al[5] found that halothane had no effect on PAM function, whereas methoxyflurane and cyclopropane did depress PAM function.

Our results are at variance with the data of Goldstein et al[5] and indicate that halothane does cause significant depression of lung antibacterial activity. One possible explanation for this may lie in the differences in the experimental protocols used. While Goldstein et al[5] anesthetized animals immediately after bacterial challenge, we allowed animals to recover from anesthesia prior to challenging them with aerosolized bacteria. Anesthesia in mice may be associated with respiratory obstruction, hypoxia, and hypercarbia. These effects may persist after the cessation of anesthesia and, if the anesthetized mice are exposed to the bacterial challenge before full recovery, additional variables may be introduced. Another explanation for the differences between our results and those of Goldstein et al[5] may be that halothane-induced depression of pulmonary bactericidal activity may require a certain length of exposure prior to its expression.

TABLE 3
Effect of Halothane on Lung Radiolabel Counts*

	No. of mice	Isotope counts at	
		0 hour	4 hours
Control	48	2,629 ± 398.8	2,288 ± 371.4
1 MAC halothane	48	2,601 ± 411.0	2,624 ± 426.4
Control	48	1,577 ± 194.2	1,479 ± 187.9
2 MAC halothane	48	1,847 ± 298.4	1,503 ± 238.1

* Values shown are means ± SE of the isotope counts of mice at 0 hour and 4 hours after exposure to aerosolized bacteria of groups A, B, C, and D (N = 24) as described in "Materials and Methods."

Halothane depresses mucociliary clearance,[15] which would be reflected in depressed physical clearance of inhaled bacteria. However, in this experiment we were unable to show any depression of mucociliary clearance by 1 or 2 MAC halothane. These results are in agreement with Goldstein et al.[5] They too were unable to show depression of physical clearance of bacteria by lungs following exposure to halothane. We have found, in a separate study[16] of ciliary activity utilizing organ culture of ferret tracheal rings, that 2 MAC halothane has no depressant action on the ciliary activity. Higher concentrations depressed ciliary activity, but recovery of ciliary activity occurred almost immediately after halothane was removed.[16] In the present experiment, we allowed the mice to recover from halothane anesthesia for 1 hour before they were challenged with aerosolized bacteria. During this time the ciliary activity can be assumed to have recovered completely, and no depression of physical clearance mechanisms of the anesthetized mice was seen.

The incidence of postoperative pulmonary infections is related to the age, sex, and smoking habits of the patient, and above all to the site and duration of the operation.[1, 2, 17] Also, the bacterial culture of bronchial secretions of the patient with postoperative pulmonary infections shows a predominance of normal bacterial flora, suggesting that the normal defense mechanisms of the lungs are impaired. We therefore conclude that it is the PAM function that is depressed postoperatively, rather than physical clearance. Postoperative pneumonia may be related to an anesthetically induced depression of pulmonary alveolar macrophage function.

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Bacterial Tracheitis

Eight infants and children, aged 3 weeks to 6 years, were observed with an acute, infectious, upper airway obstructive disease with features common to both croup and epiglottitis. The authors have termed this distinct entity "bacterial tracheitis." All patients failed to respond to treatment for croup, including racemic epinephrine delivered by intermittent positive-pressure breathing. Direct laryngoscopy consistently revealed a normal epiglottis and aryepiglottic folds but marked subglottic mucosal edema. Tracheal suctioning yielded copious mucopus below the subglottic swelling. Cultures of this material grew *Staphylococcus aureus* (six), group A *Streptococcus* (one), and *Haemophilus influenzae* (one). All patients required periodic tracheal suctioning for relief of upper airway obstruction. Six patients required endotracheal intubation; one required a tracheostomy. Bacterial tracheitis should be considered in the differential diagnosis of a young child with a croup-like illness that is refractory to conventional therapy. *(Jones R, Santos JI, Overall JC Jr: Bacterial tracheitis. JAMA 242:721-726, 1979)*

SPECIAL
article

Adrenergic Receptors and Others

Fourteenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture

Raymond P. Ahlquist, PhD, FCP*

THE STUDY of drug receptors has proved to be a most fruitful field as far as clinical medicine is concerned. Not too many years ago pharmacologists and physicians had to memorize all of the many effects that each single drug could produce. It was not too apparent that drugs of similar molecular shape could have related and predictable effects.

Receptor pharmacology is based on the principle that communication between cells in the living organism is carried out by chemical messengers. The tissue such as a gland or nerve end originating the message releases a specific chemical substance that we term a transmitter or hormone. This transmitter is carried by the blood or other tissue fluid to the cell that is going to respond. Only cells that have the proper receptor can respond to the transmitter.

The receptor has two main functions. First it has an affinity for the molecular shape and conformation of the transmitter. This results in a binding of the transmitter and the receptor. Second, the binding may trigger a response of the tissue. The binding or recognition step is unique for each hormone or transmitter. The second step is shared by many transmitters since only a go or no-go response can occur in the tissue.

Chemicals other than the natural transmitters can also act on these receptors. Some are agonists; the binding to the receptor triggers a response. Some are blocking agents; binding is not followed by a response but agonists are prevented from binding. There probably are no such things as drug receptors. Drugs that are not natural transmitters act only on receptors that are present to respond to a natural transmitter or hormone. Therefore, it is necessary to establish what receptors are naturally present.

Receptors are known for all of the endocrine hormones; these will not be considered further. It is the receptors for neurotransmitters that will be considered. How many receptors are there? The simple answer is: there are as many receptors as there are transmitters. Several transmitters are well established. These include norepinephrine and acetylcholine. Several substances are reputed to be transmitters such as histamine and the endorphins. I am indebted to Professor Breathnach of Ireland[1] for the following criteria that must be met to prove that a substance is a transmitter (humour) and not just a rumour. And if it is a transmitter it must have a receptor:

1. The released transmitter must be detectable. This is often difficult because of rapid removal, usually by neuronal re-uptake.
2. Administration of the transmitter should duplicate the action of released transmitter. This may not always occur because the exact site of release cannot easily be duplicated.

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3. The transmitter should be stored in high concentration at the site of release.
4. The proper enzymes needed for the biosynthesis of the transmitter must be present.
5. The transmitter removal rate should parallel the decline in receptor response.
6. Any interference with the biosynthesis, storage, release, or re-uptake should produce the expected response.
7. The receptor blocking agents should have the same effect on released transmitter and administered transmitter.

There are at least 15 "humours and rumours" and associated receptors in the central nervous system. Because of structural complexity and experimental difficulties these have not as yet been sorted out completely. In the periphery there are only two proved neurotransmitter systems. These are the cholinergic systems and the adrenergic system. In addition there are receptors for histamine, serotonin, dopamine, and angiotensin.

When the chemist makes analogues of a transmitter, compounds are found that may have any of the following pharmacodynamic actions: (1) Some compounds are agonists being more or less potent than the transmitter. (2) Some are blocking agents that bind to the receptor but produce no response. (3) Many are inactive having no effect on the receptor. (4) Some act selectively, as agonists or blocking agents, on only some receptors of a given type.

Some of the important receptors will be considered from three viewpoints: pharmacologic, biochemical, and clinical.

Adrenergic Receptors

Pharmacology

These receptors are the site of action of the sympathetic neurotransmitter norepinephrine. Epinephrine, the adrenal medullary hormone, also acts on these receptors. Generally speaking epinephrine is the more potent agonist.

Epinephrine produces a great variety of effects: vasoconstriction, vasodilation, cardiac stimulation, bronchodilation, lipolysis, glycogenolysis, platelet aggregation, myometrial contraction or relaxation, splenic contraction, and intestinal relaxation. Derivatives of epinephrine produce the same effects, more or less.

In 1948 as the result of a comparative, quantitative study of several catecholamines closely related to epinephrine, we postulated the existence of two different adrenoceptors, alpha and beta.[2] Adrenergic agonists could now be classified as either alpha agonists or beta agonists. The drugs that were then classified as sympatholytics actually are alpha blocking agents. The beta blocking agents were discovered in 1958; at present there are about fifteen beta blockers used clinically around the world.

Some of the clinically important adrenergic receptors are listed in Table 1. The characteristics of all of these receptors have been proved by the use of agonists and blocking agents. For example, epinephrine produces all of the adrenergic responses. Following an alpha blocker epinephrine produces only the beta effects. Following a beta blocker epinephrine produces only the alpha effects. The effects of norepinephrine released by adrenergic nerves is similarly modified by the blocking agents.

Biochemistry

Utilizing specific, high affinity, high specific radioactive ligands, the adrenergic receptors have been labeled.[3] For example, the tritiated form of dihydroergocryptine has a high affinity for alpha adrenergic receptors. The prior addition of alpha agonists or blocking agents will compete with this binding. It is, therefore possible to quantitate the binding affinities of the agonists and blocking agents. The results obtained confirm in general the affinities previously estimated from pharmacologic dose-response measurements.

Epinephrine has the greatest affinity for alpha receptors followed by norepinephrine, dopamine, phenylephrine, metaraminol, methoxamine, and ephedrine. Isoproterenol, as would be expected from its

TABLE 1

Classification of Some Adrenergic Receptors

Alpha	Beta
Smooth muscle contraction	Smooth muscle relaxation
Blood vessels	Bronchi
Iris dilator	Myometrium
Spleen capsule	Blood vessels
Myometrium	Gut
Smooth muscle relaxation	Cardiac stimulation
Gut	Increase rate
Pancreas	Increase force
Decrease insulin secretion	Increase conduction
	Pancreas
	Increase insulin secretion
	Kidney
	Increase plasma renin

structure, has a relatively high affinity for alpha receptors. However, its potency as an alpha agonist is low because of its high affinity and potency on beta receptors.

The alpha blocking agents can be arranged in the following descending order of affinity: dihydroergotamine, phentolamine, phenoxybenzamine, ergotamine, and tolazoline. Propranolol has only slight affinity for alpha receptors.

The beta adrenergic receptor can be labeled using the tritiated form of dihydro-alprenolol. The relative affinities of beta agonists are: isoproterenol > epinephrine > norepinephrine. The beta receptor has also been studied using a radioactive agonist, tritiated hydroxy-benzyl-isoproterenol. The relative affinities of the beta agonists are as follows: isoproterenol > epinephrine > norepinephrine > dopamine.

The relative binding affinities of the beta blocking agents are directly related to their activity in preventing adenyl cyclase activation of beta agonists.

Clinical

The clinical effects of some of the adrenergic drugs are shown in Table 2. Some of these effects are used for therapeutic purposes. Other effects are often regarded as unwanted adverse actions.

The alpha adrenergic blocking agents have been used clinically in the diagnosis and medical treatment of pheochromocytoma. Biochemical tests for catecholamine metabolites have generally replaced the phentolamine blood pressure test. Phentolamine is still used during surgical removal of the tumor(s). Phenoxybenzamine given orally is occasionally used to treat some patients with pheochromocytoma.

These classic alpha blockers were relatively useless as antihypertensive agents. The reflex cardiac stimulation induced by their depressor action was unacceptable by the patients. With the development of beta blockers as antihypertensives (see below) these adverse effects of alpha blockade can be overcome. The alpha blockers will make a comeback as antihypertensives. In fact, in Europe a drug called labetolol, which blocks adrenergic receptors, is used clinically as an antihypertensive agent.

Prazosin is a new compound recently released in the United States.[4] Originally thought to be a nonselective vasodilator, it is now known to be a unique, effective alpha blocking agent. Like the classic alpha blocking agents prazosin reverses the epinephrine pressor response, blocks the norepinephrine pressor response, and does not change the responses to angiotensin or vasopressin. Unlike the other alpha blockers prazosin does not increase the release of norepinephrine from the nerve end. It is thought that prazosin does not act on prejunctional alpha receptors (known by some as alpha$_2$); activation of these receptors inhibits the release of norepinephrine by the nerve action potential. Thus, prazosin produces less reflex cardiac stimulation and renin release.

The total hemodynamic effect of prazosin is a fall in arterial pressure, a decrease in arterial resistance, an increase in venous capacity, and only a slight change in heart rate, cardiac output, and right atrial pressure. In addition to being used as an antihypertensive, with or without a beta blocker, prazosin will

TABLE 2
Clinical Effects of Some Adrenergic Drugs

Adrenoreceptor	Alpha	Beta$_1$	Beta$_2$
Agonists*	Phenylephrine Dopamine Vasoconstriction Mydriasis Gut relaxation	Isoproterenol Dopamine Dobutamine Cardiac stimulation Renin release	Isoproterenol Dopamine Terbutaline Vasodilation Bronchodilation
Blocking agents†	Phentolamine Phenoxybenzamine Prazosin Postural hypotension Miosis Antihypertensive Decrease cardiac pre-load	Propranolol Timolol Metoprolol Bradycardia Lengthen P-R interval Decrease renin release Antihypertensive Decrease intraocular pressure	Propranolol Timolol Bronchoconstriction Increase peripheral resistance

* Epinephrine and norepinephrine are specific agonists for both receptors.
† Labetolol blocks all adrenoceptors.

have a use in severe congestive failure by decreasing cardiac pre-load and after-load.

There are least two different types of beta adrenoceptors. Type 1 is associated with cardiac stimulation, lipolysis, and renin release. Some beta blockers act selectively on beta_1 receptors. Metoprolol, for example, may be safer than propranolol in patients with obstructive lung disease. Type 2 is associated with smooth muscle relaxation. Terbutaline, a selective beta_2 agonist, produces less cardiac stimulation than isoproterenol when used in bronchial asthma.

Dopamine

Dopamine is the immediate precursor of norepinephrine. There is considerable evidence that this catecholamine is a transmitter in the central nervous system. In the periphery dopamine has several different actions; it is an alpha receptor agonist, a beta receptor agonist; it can enter adrenergic nerve ends to displace stored norepinephrine; and it acts on specific dopamine receptors to produce vasodilation in the renal and mesenteric vascular beds. Dopamine receptors are selectively blocked by tranquilizers such as haloperidol.

Dopamine is used clinically to treat intractable heart failure. Its advantage is the relative lack of renal vasoconstriction. Its most serious disadvantage is peripheral vasoconstriction produced by large doses.

Dobutamine

This catecholamine has recently been approved by the Food and Drug Administration (FDA) for the treatment of acute cardiac failure.[5] It is related chemically to both dopamine and isoproterenol. Dobutamine is mainly a beta_1 adrenoceptor agonist producing positive inotropic and chronotropic actions on the heart. For some reason it produces little increase in heart rate in man.

Dobutamine has only a slight action on alpha receptors, a slight action on beta_2 receptors, and no action on dopamine receptors.

Receptor Modification

It has long been known that receptors are changed by changes in the environment of the tissue. A classic example is the apparent difference of the adrenoceptor of myometrium in the pregnant and nonpregnant state. The virgin cat has beta receptors; the pregnant cat has alpha receptors.

One clinical example of receptor modification is the effect of hyperthyroidism on cardiac beta receptors. In this disorder the tachycardia is due to an increased beta response and is not due to increased sympathetic action.

The response to many autonomic drugs changes when the drug is continuously administered. For example, asthmatics become resistant to the bronchodilator action of the beta adrenoceptor agonist isoproterenol. Until fairly recently these observations were difficult to explain.

It is now possible to measure the number of adrenoceptors in a given tissue using radioactive binding agents. It has been found that the administration of a large amount of a beta agonist reduces the number of beta adrenoceptors. Conversely, the continued administration of a beta blocker increases the number of beta adrenoceptors. In hyperthyroidism the number of cardiac beta receptors is increased. And it has been found that estrogen increases the number of alpha receptors of uterine muscle.

These findings have important clinical significance. One example is the difficulty in withdrawing adrenergic vasoconstrictors used to maintain adequate arterial pressure. It is probable that continuous activation of alpha receptors reduces their number. Therefore, when the alpha agonist is withdrawn the blood vessels cannot respond adequately to sympathetic control. Another example is the apparent increase in incidence of myocardial infarction when beta blockers are suddenly withheld from angina patients. Withdrawal of the beta blocker would result in cardiac supersensitivity.

Beta Blockers

The beta blockers are of particular interest to anesthesiologists. These drugs are rapidly becoming agents of first choice in the treatment of hypertension. Most patients with angina are being treated with beta blockers. Thyrotoxic patients are prepared for surgery with beta blockers. The drugs are also used to treat anxiety and migraine even though these indications are not approved by the FDA. One beta blocker, timolol, is rapidly becoming the drug of choice to lower intraocular pressure. Even though timolol is used only in the form of eye-drops its potency is such that there is a real possibility of systemic action.

Should beta blockers be discontinued prior to anesthesia? If they are not discontinued what are the possible drug interactions that may occur? There is no compelling pharmacologic reason to discontinue these drugs. In fact, as noted above, the sudden withdrawal may be dangerous. There are several drug interactions that occur. Some of these are listed in Table 3. Since the block is competitive in nature the response to the agonists can be restored by increasing the dose.

Cholinergic Receptors

Pharmacology

There are three peripheral cholinergic receptors. They are differentiated by anatomical location and by selective agonists and blocking agents. Structures innervated by postganglionic cholinergic nerves have *muscarinic* receptors. Structures innervated by preganglionic nerves have *ganglionic* (nicotinic) receptors. Skeletal muscle has *somatic* (nicotinic) receptors. Table 4 reviews some of the responses controlled by cholinergic receptors.

The cholinergic agonists and blocking agents are quite selective. Within certain limits their actions are confined to only one type of receptor. Bethanechol and atropine act on muscarinic receptors; dimethylphenyl-piperzinium (DMPP) and mecamylamine act on ganglionic receptors; and succinylcholine and tubocurarine act on somatic receptors. The cholinesterase inhibitors such as neostigmine can activate all cholinergic receptors.

TABLE 3
Drug Interactions with Beta Blockers

Increased effectiveness	Decreased effectiveness	No change in effectiveness
Vasoconstriction Epinephrine Norepinephrine Dopamine	Cardiac stimulation Isoproterenol Epinephrine Norepinephrine Dopamine Dobutamine Bronchodilation Isoproterenol Epinephrine Terbutaline Vasodilation Isoproterenol Dobutamine	Vasoconstriction Angiotensin II Cardiac stimulation Digitalis Glucagon

TABLE 4
Classification of Cholinergic Receptors

Muscarinic	Ganglionic	Somatic
Smooth muscle contraction Iris sphincter Ciliary Bronchi Gut Smooth muscle relaxation Blood vessels Heart Decrease rate Decrease conduction Glands, lacrimal, salivary, etc Secretion	Total autonomic activation Epinephrine release	Skeletal muscle contraction

Biochemistry

Most studies of the chemical nature of cholinergic receptors have been carried out on somatic receptors. The electroplax of the electric eel is a favorite cell to study. The cholinergic receptors are discrete areas readily depolarized by acetylcholine. The depolarization then spreads over the rest of the membrane. Somatic receptors are localized at the motor end plate.

Clinical

The clinical effects of some cholinergic agonists and blocking agents are shown in Table 5. In general muscarinic receptors and adrenergic receptors produce opposite effects. For example, a muscarinic receptor produces bradycardia and an adrenergic receptor produces tachycardia. This relationship is of importance in predicting what response will occur when a receptor blocking agent is administered; atropine may not increase heart rate in the presence of beta adrenergic blockade.

Ganglionic agonists are pharmacologic curiosities. Since they produce total autonomic activation it is difficult to predict what effects will be seen. Nicotine seems to produce mainly sympathetic effects: vasoconstriction, pressor, tachycardia. Many of the responses to cholinesterase inhibitors such as neostigmine also result from ganglionic stimulation.

Ganglionic blocking agents have only limited therapeutic use because they produce a total autonomic "denervation." Some of these drugs have been used in peptic ulcer and essential hypertension; however, because of side effects they are seldom used.

Histamine Receptors

The exact role of histamine in the body is not clear. Occurring in mast cells and other tissues it produces a variety of important physiologic responses. It is now known that there are two histamine receptors, H_1 and H_2. Some of the responses associated with each of these is shown in Table 6.

The classic antihistamines such as diphenhydramine block only the H_1 receptors. Therefore, these drugs do not block HCl secretion induced by histamine and cannot completely block the depressor response to histamine.

TABLE 5
Clinical Effects of Cholinergic Drugs

	Muscarinic	Ganglionic	Somatic
Agonists*	Pilocarpine Bethanechol Miosis Ciliary spasm Vasodilation Bradycardia Gland secretion	DMPP† Nicotine Miosis Mydriasis Vasoconstriction Bradycardia Tachycardia	Succinylcholine Twitch-paralysis
Blocking agents	Atropine, etc Mydriasis Cyclopegia Tachycardia Decrease secretion	Mecamylamine Cycloplegia Postural-hypotension	Tubocurarine Paralysis

* Acetylcholine is the agonist for all cholinergic receptors.
† DMPP, dimethyl-phenyl-piperzinium. This is not a useful drug.

TABLE 6
Histamine Receptors

	H_1	H_2
Agonists	Histamine 2-Methyl histamine* Smooth muscle contraction Bronchi Blood vessels Vasodilation Capillaries Venules	Histamine 4-Methyl histamine* Gastric glands Stimulate HCl secretion Vasodilation Capillaries Venules
Blocking agents	Diphenyldramine, etc	Cimetidine

* Not used clinically.

Cimetidine, a recently released drug, is representative of a new class of antihistamines, the H_2 receptor blockers.[6] This drug blocks some of the depressor response to histamine and blocks the stimulation of gastric acid secretion by histamine, pentagastrin, and acetylcholine. Cimetidine is useful in the treatment of peptic ulcer, gastric hemorrhage, pancreatic insufficiency, and Zollinger-Ellison syndrome. This drug has also been found to be effective in controlling gastric hypersecretion in the short-bowel syndrome.[7]

It is now possible to completely block all of the effects of histamine released from most cells. For example, the flush associated with metastatic carcinoid can be prevented by a combination of diphenhydramine and cimetidine.[8] This combination should also be effective in controlling the response to histamine released by tubocurarine.

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CLINICAL reports

Profound Hypotension following a "Test Dose" of Bretylium Tosylate

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Bretylium tosylate is a quarternary ammonium compound that has recently been released for the treatment of life-threatening ventricular arrhythmias. Marked hypotension can develop in patients with compromised cardiac function who are given therapeutic doses of bretylium. We recently encountered a patient with cardiac failure following cardiopulmonary bypass who developed severe supine hypotension following a "test dose" of bretylium.

Case Report

A 72-year-old man was admitted for coronary artery bypass grafting and aortic valve replacement. Past history included an episode of acute tubular necrosis, hypertension of 15 years duration, adult onset diabetes mellitus controlled by diet, and an episode of mild congestive heart failure following a blood transfusion. Cardiac catheterization revealed triple coronary artery disease, left ventricular anterior wall dyskinesis, an aortic valve area of 0.7 cm^2, and a pressure gradient across the aortic valve of 50 torr. A Holter monitor worn a month before admission showed up to 30 multifocal ventricular contractions per minute. Quinidine was prescribed and later changed to procainamide immediately before admission because of a suspected hemolytic reaction. The procainamide was discontinued several days preoperatively because of a febrile reaction. Other medications included furosemide, 20 mg daily, isosorbide, 15 mg orally every 6 hours, KCl, and nitroglycerin.

The patient was premedicated with morphine sulfate, 6 mg, and scopolamine, 0.3 mg IM. General anesthesia consisting of morphine, diazepam, nitrous oxide, and oxygen was administered with sodium nitroprusside to control systemic vascular resistance. Following myocardial revascularization and aortic valve replacement, the patient required atropine, 1 mg, calcium chloride, 1 gm, and metaraminol, 2 mg, in divided doses to achieve a sinus rhythm and stable blood pressure. Cardiac output following cardiopulmonary bypass was 5.5 L/min and systemic vascular resistance was 1250 dynes/sec/cm^{-5}.

Over the next 2 hours the patient developed multifocal premature ventricular contractions increasing to 20 to 30/min. Systolic blood pressure ranged from 80-130 torr with a heart rate 80-100 beats min. Repeated doses of intravenous lidocaine (350 mg over 45 minutes) did not improve the arrhythmias. Neither atrial nor ventricular pacing abolished the premature contractions. Cardiac output decreased to 1.9 L/min and systemic vascular resistance increased to 4000 dynes/sec/cm^{-5}. Sodium nitroprusside and epinephrine infusions restored cardiac output to 3.35 L/min and lowered resistance to 2626 dynes/sec/cm^{-5}. Pulmonary artery pressure was 25/15 torr and central venous pressure 14 torr. Arterial blood sample revealed pH 7.53, P_{O_2} 351 torr, P_{CO_2} 31 torr, with serum K$^+$ 4.6 mEq/L, Na$^+$ 144 mEq/L, and hematocrit 31%. A therapeutic dose of bretylium tosylate was calculated to be 400 to 800 mg (5 to 10 mg/kg); however, a "test dose" of 100 mg was given over 30 seconds through the central venous pressure line of a Swan-Ganz catheter (see Figure). Systemic arterial pressure immediately decreased from 120 torr to 50 torr. Calcium chloride, 500 mg, was given without significant change in blood pressure. A bolus injection of epinephrine, 12 μg, restored the blood pressure, and cardiac output stabilized at 5.06 L/min with systemic vascular resistance of 1310 dynes/sec/cm^{-5}. The arrhythmias, however, persisted until the day after surgery when disopyramide phosphate was given. The patient was discharged in good condition 11 days after the operation.

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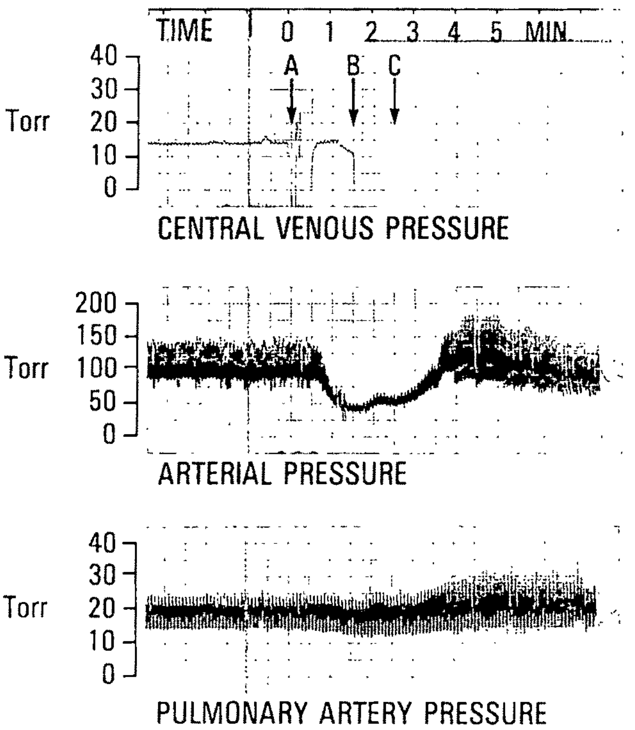

FIGURE. Severe hypotension following a "test dose" of bretylium tosylate. All injections made through central venous port of Swan-Ganz catheter: A, bretylium, 100 mg; B, calcium chloride, 500 mg; C, epinephrine, 12 μg.

Discussion

The effects of bretylium tosylate on ventricular arrhythmias have been studied extensively, and the drug has recently been marketed in the United States for this use. Bretylium increases fibrillation threshold in normal and ischemic animal hearts and prevents many experimentally induced arrhythmias.[1,2] Adrenergic actions of the drug are complex and unpredictable. Release of norepinephrine from sympathetic nerve endings may be caused by high concentrations of bretylium and may result in transient hypertension and tachycardia.[3] Subsequently, and in lower concentrations, bretylium inhibits release of norepinephrine and thus acts as a sympathetic blocking agent.[3] In addition, reuptake of epinephrine and norepinephrine into nerve endings may be inhibited, and thus the actions of these amines may be potentiated.[4] The relative importance of these adrenergic actions in any given patient depends on the dose of bretylium employed, on the patient's preexisting rate of sympathetic discharge, and on the level of circulating catecholamines.[5] Seventy to 80% of an intravenous dose is excreted unchanged in the urine within 24 hours.[6] Bretylium is approved only for parenteral use in the United States. Recommended dosage is 5 to 10 mg/kg given intravenously over 10 minutes or administered intramuscularly for treatment of refractory ventricular arrhythmias. During ventricular fibrillation, a rapid intravenous injection of 5 mg/kg may be given; the maximum recommended dose is 30 mg/kg.

The treatment of life-threatening ventricular arrhythmias involves correction of any contributing metabolic abnormality such as acidosis or hypokalemia and the use of cardioversion or intravenous lidocaine or procainamide.[7] When these drugs are contraindicated or ineffective, alternatives include diphenylhydantoin, propranolol, quinidine, disopyramide, electrical pacing, and bretylium.[8] Several studies have indicated that bretylium can stabilize cardiac rhythm in about half of patients with resistant ventricular fibrillation or recurrent ventricular tachycardia that has not responded to other treatment.[9-11] In the majority of patients, bretylium causes a modest decline in blood pressure due to its sympathetic blockade. However, in patients with severely compromised cardiac function clinically significant decreases in blood pressure may follow therapeutic doses.[11-13] The dramatic decrease in blood pressure that we observed after so small a dose of bretylium was unexpected. Although we cannot be certain of the mechanism, we feel the most likely cause was sympathetic blocking action of the drug in a patient with little myocardial reserve.

Use of bretylium in the operating room should be restricted to ventricular arrhythmias which are refractory to standard modes of therapy. This report further cautions that a relatively small "test dose" of bretylium, given intravenously, may produce profound hypotension.

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Intrathoracic Pressure and Left Ventricular Performance

Left ventricular dysfunction is common in respiratory distress syndrome, asthma, and obstructive lung disease. To understand the contribution of intrathoracic pressure to this problem, the effects of Valsalva and Müller maneuvers on left ventricular function were studied in eight patients. Implantation of intramyocardial markers permitted beat-by-beat measurement of the velocity of fiber shortening (V_{CF}) and left ventricular volume. During the Müller maneuver, V_{CF} and ejection fraction decreased despite an increase in left ventricular volume and a decline in arterial pressure. In addition, when arterial pressure was corrected for changes in intrapleural pressure during either maneuver it correlated better with left ventricular end-systolic volumes than did uncorrected arterial pressures. These findings suggest that negative intrathoracic pressure affects left ventricular function by increasing left ventricular transmural pressures and thus afterload. The authors conclude that large intrathoracic-pressure changes, such as those that occur in acute pulmonary disease, can influence cardiac performance. *(Buda AJ, Pinsky MR, Ingels NB Jr, et al: Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 301:453–459, 1979)*

ANESTH ANALG
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Intraoperative Transection of a Swan-Ganz Catheter

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Indications for use of balloon-tipped flow-directed catheters inserted into the pulmonary artery include measurement of left ventricular function and partial pressure of oxygen in mixed venous blood. However, use of the catheter has associated risks.[1] We describe the previously unreported complication of surgical transection of a Swan-Ganz catheter.

Case Report

A 58-year-old woman was scheduled for total laryngectomy and right radical neck dissection following a biopsy diagnosis of squamous cell carcinoma of the vallecula. A month previously the patient had been admitted to the hospital in congestive heart failure. She had responded well to treatment with diuretics and digitalis. The patient had a 50-pack year history of smoking. Pulmonary function studies and chest x-ray were compatible with a diagnosis of chronic bullous obstructive pulmonary disease.

Since this patient had significant heart and lung disease, and the potential for blood loss was large, a Swan-Ganz catheter was passed, via a Cordis introducer in the right cephalic vein, into the pulmonary circulation without difficulty. The Cordis port was used for fluid infusion, the right atrial port was used for drug infusion, and the pulmonary artery port was used for measuring pressure. Following tracheostomy under local anesthesia, general anesthesia was induced and maintained with 1.0 to 2.0% halothane, nitrous oxide 3 L/min and oxygen 2 L/min. Following laryngectomy, deeper invasion of the carcinoma was recognized, necessitating a partial pharyngectomy. Due to the more extensive resection, a delta-pectoral flap was raised. During the dissection in the subclavicular region, the surgeons encountered a "calcific vein" which was ligated between proximal and distal clamps. Simultaneously the previously phasic pulmonary artery pressure pattern became a straight line and "catheter fault" appeared on the cardiac output computer screen. Prompt investigation revealed the ligated cephalic vein contained a transected Swan-Ganz catheter. The clamps had not been removed and the distal fragment was easily extracted. The patient suffered no ill effects and made an uneventful recovery.

Discussion

Prompt recognition of the transection of the Swan-Ganz catheter in this case prevented a possible major complication. Embolization of catheter fragments has not been reported with the Swan-Ganz catheter. Fracture of the catheter has been reported, but embolization was prevented because the thermistor wires remained intact.[2] Several reports have described problems resulting from embolized fragments of indwelling peripheral venous, central venous, and cardiac catheters.[3-6] Death has been caused both by septic endocarditis and by perforation of the heart following embolization of catheter fragments.[3]

In this case the site of entry of the Swan-Ganz catheter was an important consideration. The internal and external jugular veins were not used because they were in the proposed surgical field. The subclavian veins were not used because of the risk of a pneumothorax in a patient with bullous pulmonary disease. The femoral veins were not used because the anterior thighs were potential skin graft donor sites. The right cephalic vein was the only prominent vein in either antecubital fossa. This means that the course of the Swan-Ganz catheter toward the heart would pass through the area involved in elevation of the delta-pectoral flap. If the anesthesiologist had warned the surgeon that the revised and extended surgical field involved the cephalic vein, transection of the Swan-Ganz catheter and the loss of fluid and drug infusion and pressure monitoring lines could have been avoided. With an increasing use of Swan-Ganz catheters and with increasingly invasive operations being performed, the potential for this complication to occur has increased. We report this case to increase awareness of this potential problem and help prevent its recurrence.

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Correlation of Preoperative Pulmonary Function with Postoperative Complications

Results of preoperative pulmonary function tests were evaluated in 106 patients who had major thoracic or upper abdominal cardiovascular surgery. These results were related to the occurrence of postoperative complications by comparison of pulmonary function data in patients with an intensive care unit (ICU) stay of less than 5 days versus patients with an ICU stay of more than 5 days. Ninety-three percent of patients had preoperative results that were considered abnormal. However, quantitative analysis of specific pulmonary function tests failed to reveal any difference in the incidence of postoperative complications between patients with modest versus severe preoperative dysfunction. The occurrence of atelectasis was related to type of cardiovascular surgical procedure, but not to preoperative pulmonary function results. Abnormalities on pulmonary function tests were not the major determinants of use of preoperative respiratory therapy, and its use was unrelated to the length of postoperative stay in the ICU. The authors conclude that prior to cardiovascular surgery, routine quantitation of clinically apparent pulmonary dysfunction may be of little value in predicting postoperative morbidity and much less important than careful clinical evaluation. When pulmonary function tests are performed in such patients, simple spirometric tests and arterial blood gas levels appear to be adequate. *(Cain HD, Stevens PM, Adaniya R: Preoperative pulmonary function and complications after cardiovascular surgery. Chest 76:130–135, 1979)*

ANESTH ANALG
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Methemoglobinemia Associated with Organic Nitrate Therapy

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Methemoglobin is formed when hemoglobin, normally in the ferrous valence (Fe^{2+}), is oxidized to the ferric valence (Fe^{3+}). Normally 99% of hemoglobin is in the reduced form and can reversibly bind with oxygen and carbon dioxide.[1] There are numerous compounds found in the environment that can oxidize ferrohemoglobin to methemoglobin which does not bind with oxygen and carbon dioxide.[2, 3] These compounds usually contain nitro or amino groups which when present in sufficient quantities overload the normal metabolic pathways that convert methemoglobin back to ferrohemoglobin. The following report illustrates a case of suspected drug-induced methemoglobinemia and the importance of direct measurement of arterial saturation and arterial oxygen tension rather than estimating oxygen saturation from oxygen tension based on a nomogram which assumes normal oxygen carrying capacity of hemoglobin.

Case Report

A 65-year-old white man was admitted to the hospital with the complaint of chest pain of 2 hours duration. A preliminary diagnosis of an impending myocardial infarction was made. Serial electrocardiograms showed an anterior ischemic pattern. Coronary angiography revealed a 70% occlusive lesion of the left anterior descending artery. The patient was given isosorbide dinitrate, 5 mg, 4 times a day, propranolol hydrochloride, 20 mg, 4 times a day, and sublingual nitroglycerin, 0.4 mg when needed. Coronary artery bypass surgery was scheduled for 1 month later. During the month prior to surgery the patient's use of sublingual nitroglycerin was infrequent (less than 0.4 mg/day). The patient was not exposed to any other known medications or potentially toxic compounds during this period. Preoperative medication included morphine sulphate, 15 mg, and hydroxyzine hydrochloride, 100 mg, intramuscularly. Prior to induction of anesthesia, the patient began to experience vague epigastric pain and was given sublingua nitroglycerin, 0.4 mg, with prompt relief of his discomfort.

After appropriate monitoring and infusion lines were established, anesthesia was induced with 10 mg of diazepam, 1 m of Innovar, and 200 mg of thiopental. Endotracheal intubation was facilitated using succinylcholine (100 mg). Anesthesia was maintained with Innovar supplemented with fentanyl and N_2O. Muscle relaxation was maintained with metocurine.

During removal of the saphenous vein, the blood in the operative field was noted to be "dark." After an intensive check of the anesthesia machine, the breathing circle, and the placement of the endotracheal tube (all of which were functioning normally) arterial blood gases were measured (sample 1 in Table). During this period the patient continued to remain hemodynamically stable. Because the blood in the operative field continued to appear unsaturated, arterial blood gases were again measured. In addition to measurement of arterial oxygen tension, carboxyhemoglobin, methemoglobin, and oxyhemoglobin levels were determined spectophotometrically using a previously calibrated IL-282 Co-oximeter (Instruments Laboratory 282 Co-Oximeter) (sample 2 in Table). After total cardiopulmonary bypass was initiated blood in the aortic cannula and oxygenator continued to appear desaturated. Arterial blood gases (sample 3 in Table) were again measured in blood from the pump and methemoglobin again determined.

Treatment of the methemoglobinemia was started at this time using 1.5 mg/kg of methylene blue administered by intravenous infusion over 10 minutes. Thirty minutes after the completion of the methylene blue infusion, the fourth sample for arterial blood gas determination was drawn (sample 4 in Table).

Results

The results of the four arterial blood gas samples are noted in the Table. In the first three samples hemoglobin desaturation was apparent as measured spectophotometrically, even in the presence of high oxygen tensions in the arterial blood. The reason for the low oxygen saturation was the high level of methemoglobin. Following therapy with methylene blue, the methemoglobin was reduced from 7.6 vol % to 2.0 vol % and the arterial saturation increased from 92% to 97%.

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TABLE

Arterial Blood Gases Values

	Sample			
	1	2	3	4
F_{IO_2}	0.5	0.5	1.0	0.5
Pa_{O_2}-torr	145	191	415	260
Pa_{CO_2}-torr	35	26	25	24
pH-log H^+	7.41	7.50	7.50	7.51
Bicarbonate meq/L	22	20	20	19
Oxyhemoglobin % (measured)	90	91	92	97
Oxyhemoglobin % (estimated)	>99	>99	>99	>99
Carboxyhemoglobin %	0.3	0.1	0.2	1.0
Methemoglobin %	...	8.0	7.6	2.0
Time	1400	1420	1440	1525

Discussion

Methemoglobin is produced from hemoglobin when the iron is oxidized to the ferric state.[1,3]

The three primary causes for the development of methemoglobinemia are: (1) An inherited autosomal recessive enzymatic deficiency of nicotinamide adenine dinucleotide-(NADH) methemoglobin reductase,[1,3] NADH-methemoglobin reductase is the enzyme in the liver which reduces the ferric iron in methemoglobin. With a decrease in the amount of methemoglobin reductase, patients are unable to rapidly convert methemoglobin to normal hemoglobin. (2) Hemoglobin M disease, an inherited autosomal dominant trait, can cause significant elevations in methemoglobin.[1,3] Hemoglobin M acts in the same physiologic manner as methemoglobin formed via an oxidation process. (3) The most frequent cause of methemoglobinemia is exposure to chemical compounds or drugs which, in large quantities, can overload the normal reduction pathways.[3-5]

The clinical manifestations of methemoglobinemia are related to symptoms attributable to hypoxemia.[1,3] Clinically recognizable cyanosis can occur with as little as 1.5 g % of methemoglobin. The severity of the symptoms are related to the quantity of methemoglobin, the rapidity of formation of methemoglobinemia, and the capacity of the patient to acclimate to the state of reduced oxygen content.[4]

In addition to the inability to combine reversibly with oxygen, methemoglobin shifts the oxyhemoglobin dissociation curve of the remaining normal hemoglobin to the left, thus making oxyhemoglobin bind more tenaciously to the available oxygen.[6] This effect is thought to reduce further the availability of oxygen at the cellular level.

Therapy depends on the severity and cause of the methemoglobinemia.[4] If there is a hereditary cause for methemoglobinemia usually no therapy is necessary. However, if the patient has symptoms of hypoxemia then daily doses of either ascorbic acid, 100 to 500 mg, or methylene blue, 100 to 300 mg, should be given. If the methemoglobinemia is secondary to a drug ingestion, the usual therapy is to remove the offending drug and the normal enzyme systems will eventually reduce the methemoglobin to normal hemoglobin. In situations in which rapid reduction in the methemoglobin is required, methylene blue, 1 to 2 mg/kg over five minutes, given intravenously and repeated in 1 hour if cyanosis persists, usually suffices.[4]

There is no evidence, based on our patient's past medical history, family history, or occupational history to suggest that the cause of the methemoglobinemia was due to acquired hemoglobin M disease or to an apparent hereditary deficiency of methemoglobin reductase. However, spectrophotometric analysis of the patient's hemoglobin was not done to confirm the presence of hemoglobin M nor was a quantitative analysis of the enzyme NADH methemoglobin reductase performed to confirm its level in this patient. The methemoglobinemia observed in our patient was most probably drug induced. Review of the drugs known to be taken by the patient suggests that the nitrates used for the treatment of chest pain were responsible, although unconfirmed.

We are unaware of any prospective study in man that associates the formation of methemoglobinemia to the therapeutic use of organic nitrates; however, this has been demonstrated in rabbits.[7] A review of a series of 25 patients in our institution who have undergone open heart surgery, 25% of whom were treated preoperatively with organic nitrates, suggests no direct correlation. There was no significant difference in the methemoglobin levels intraoperatively between patients treated with organic nitrates and those not treated. All of the patients' intraoperative levels of methemoglobin were within normal limits; however, this was a small sample and would not reveal the occasional patient whose reduction pathways were overloaded with nitrates. Recently we have experienced another unsuspected case of methemoglobinemia in a patient treated with organic nitrates prior to coronary artery bypass surgery. Although these data are inconclusive we feel that a prospective study in man relating the use of organic nitrates to the development of methemoglobinemia should be performed.

The inability to measure oxygen saturation and methemoglobin would have made the diagnosis of the cause of the desaturated appearing blood difficult. The high oxygen tensions would have suggested that this patient's hemoglobin was completely saturated with oxygen when in fact the saturation was diminished. Oxygen saturation obtained from a nomogram would have been inaccurately estimated. (Table).

It can be debated whether therapy was necessary for the level of methemoglobinemia observed in our patient. However, we chose to treat the patient in anticipation of the possibility of a lower arterial tension following extubation which may occur in these patients.

In summary, it is important in patients given nitrates to measure not only the arterial oxygen tension, but also to measure directly arterial oxygen saturation and its contributing levels of deoxyhemoglobin, carboxyhemoglobin and methemoglobin rather than estimating oxygen saturation from a nomogram which assumes normal oxygen carrying capacity of hemoglobin. In addition, it is important to be aware that the nitrate compounds used in the treatment of coronary artery disease may reduce the oxygen carrying capacity of the blood by the formation of methemoglobin.

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Epidural Analgesia Inhibits Stress Response

Plasma renin activity and aldosterone concentration, and urinary sodium and potassium excretion were measured over a 24-hour period in 12 patients undergoing abdominal hysterectomy. Six patients received general anesthesia with thiopental, N_2O-O_2, halothane. Postoperatively analgesics were administered as required. The second group of six patients received epidural analgesia, with a block from T4 to S5 maintained for 24 hours. The normal stress-induced increase in plasma renin activity and aldosterone concentration was absent in the group given epidural analgesia. Urinary potassium excretion was lower in the group given epidural analgesia, but sodium and water balance was similar in the two groups. The mechanism by which epidural analgesia modifies the response to stress is uncertain. *(Brandt MR, Olgaard K, Kehlet H: Epidural analgesia inhibits the renin and aldosterone response to surgery. Acta Anesthesiol Scand 23:267–272, 1979)*

ANESTH ANALG
58:524-525, 1979

Severe Hypertension and Multiple Atrial Premature Contractions following Naloxone Administration

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Ventricular fibrillation,[1] hypertension,[2] and pulmonary edema[3] have been reported following naloxone. We report here severe hypertension and multiple atrial premature contractions (APCs) following administration of this drug.

Case Report

A 73-year-old man was found to have "sick sinus syndrome" (sinus bradycardia, sinoatrial block, and sinus arrest[4]) after experiencing several episodes of syncope and loss of consciousness. A transvenous demand pacemaker was inserted under local anesthesia without complications. He was scheduled for insertion of an epicardial pacemaker under general anesthesia after pacemaker malfunction was detected during a routine check-up 3 months later.

Physical examination prior to surgery revealed no abnormalities. Blood pressure was 140/80 torr; the pulse was regular at 70 beats/min with occasional episodes of asymptomatic bradycardia at 56 beats/min. Blood chemistries and electrolytes were normal. The ECG showed ventricular pacing at 70 beats/min with occasional pacing failure and spontaneous appearance of sinus bradycardia at 56 beats/min.

The patient arrived in the operating room without premedication. A peripheral intravenous cannula was inserted and blood pressure cuff and ECG electrodes were placed. After 3 minutes of preoxygenation, anesthesia was induced with fentanyl citrate, 0.2 mg, and sodium thiopental, 300 mg IV. Tracheal intubation was facilitated with succinylcholine, 100 mg IV, and anesthesia was maintained with nitrous oxide, 70% in oxygen. Ventilation was controlled at a tidal volume of 600 ml at 10 breaths per minute. Blood pressure rose to 170/95 from 140/80 torr after tracheal intubation. Since intermittent increments of droperidol to a total of 7.5 mg failed to control blood pressure it was decided to continue maintenance of anesthesia with enflurane 1 to 2%. Systemic blood pressure fluctuated between 120/60 and 160/80 torr for the next 90 minutes. Lactated Ringer's solution, total 200 ml, was administered during surgery.

The patient remained unresponsive 30 minutes after discontinuing enflurane. Since the respiratory rate was 6 to 8/min and the pupils pin-point, a residual effect of fentanyl was suspected and naloxone, 0.4 mg, was given intravenously. The patient regained consciousness and respiratory rate increased almost immediately. The endotracheal tube was removed thereafter and the patient taken to the recovery room.

On admission to the recovery room the patient was incoherent and restless. Blood pressure was 200/120 torr. Diazepam, 5 mg, given to sedate the patient, was to no avail. The possibility of incoherence due to droperidol was then considered and physostigmine, 2 mg, was given intravenously, as recommended by Bidawi et al.[5] The patient became more lucid and cooperative, but blood pressure increased to 270/140 torr and multiple APCs were seen on the ECG. Arterial blood gases at this time while breathing room air were pH 7.41, P_{O_2} 80 torr, P_{CO_2} 36 torr. Arterial and central venous lines were inserted. Infusion of sodium nitroprusside, up to 200 mg/min, was required during the following 8 hours to maintain blood pressure at 150 to 160/80 to 90 torr.

Blood pressure remained 120/70 to 140/70 torr without antihypertensive drugs during the remainder of the patient's hospital stay. A week later the patient was discharged.

Discussion

Pain, anxiety, fluid retention, distended bladder, pheochromocytoma, and clonidine (Catapress) withdrawal[6] are some of the possible causes of acute postoperative hypertension. None of these causes was believed to be operating to elevate this patient's blood pressure.

Naloxone is widely believed to be a safe drug with minimal side effects. If given without antecedent narcotics it is said to exhibit essentially no pharmacologic activity.[7] Hypertension and tachycardia have been reported after large doses but this generally is believed to be due to reversal of analgesia. Review of the literature does not bear this out. Tanaka[2] reported a case of pressor response to 340/150 torr with paroxysmal atrial tachycardia which started during slow

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intravenous injection of 0.4 mg of naloxone and which reached a peak in 10 minutes. Flacke, et al,[3] reported hypertension and severe pulmonary edema immediately after naloxone 0.4 mg IV was administered to reverse 136 mg of morphine given during open heart surgery. Michaelis et al[1] reported two cases of ventricular fibrillation following naloxone. In one patient, fibrillation occurred after only 0.1 mg of naloxone. The view that reversal of analgesia is not the cause of the hypertensive response seems to be strongly supported by the observations of Patschke et al.[8] Dogs anesthetized with halothane and nitrous oxide were given intravenous morphine followed by reversal doses of naloxone while anesthesia was maintained. Significant rise in systemic blood pressure rapidly followed the naloxone. Naloxone appears to have a pressor effect unrelated to narcotic reversal.

The mechanism of hypertensive reaction after naloxone can only be speculated. Small doses of narcotics increase adrenergic activity as a result of catecholamine release.[9] Freye[10] postulates that naloxone competes with narcotics for identical receptor sites in the central nervous system, displaces some of their molecules, and thus precipitates the "small dose effect" of narcotics.

Although cardiovascular diseases seem to be common to all cases reported, it is possible that the naloxone-induced pressor responses may be missed in patients without preexisting cardiovascular diseases because vascular monitoring is usually not as intense in such patients. The cardiac response to hypertension appears to depend on the patient's underlying cardiac state: Those with compromised left ventricular function are likely to develop ventricular fibrillation[1] or pulmonary edema[3]; patients with good ventricular function are more likely to develop supraventricular irritability (Tanaka[2] and our patient).

Because naloxone is widely believed to be innocuous, large maintenance doses of narcotics are commonly used with the expectation that reversal can be achieved safely at the end of anesthesia. This may not always be the case, especially in patients with coronary disease. Pronounced pressor responses may be seen with as little as 0.1 mg of naloxone injected slowly.[1] Also, reestablishment of analgesia after naloxone reversal of analgesia may prove difficult and may require a large amount of narcotic. Flacke's patient, for example, required 30 mg of morphine to be quieted after naloxone.[3]

Following naloxone administration, arterial blood pressure should be monitored closely for at least 10 minutes and antihypertensive drugs should be immediately available.

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ANESTH ANALG
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Blood Pressure Monitoring Using the Superficial Temporal Artery and a Doppler Ultrasonic Flow Detector

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Blood pressure monitoring, a prerequisite to safe anesthetic practice, may be accomplished by intraarterial cannulation, by the Riva-Rocci method employing a stethoscope for detection of the Korotkoff sounds, or by a Doppler ultrasonic flow detector.[1,2] The Doppler ultrasonic flow detector is particularly useful in patients whose arterial walls do not generate sufficient sound to be heard by a stethoscope and in whom technical difficulties preclude direct arterial cannulation. Commonly, the brachial or radial arteries are chosen for blood pressure monitoring, but the femoral, popliteal, tibial, and dorsalis arteries have also been used.

Recently, during the anesthetic management of a patient whose blood pressure could not be monitored at any conventional site, an alternate method was devised using the temporal artery.

Case Report

A 68-year-old woman was scheduled for exploratory surgery of an occluded right axillobifemoral bypass graft which had been performed 2 years earlier. She was a chronic smoker and had diabetes of long standing duration treated with diet and tolbutamide. Other medications included codeine, acetaminophen, and amitriptyline. Significant physical findings were limited to bilateral calf tenderness and absence of detectable pulse in the left arm and both lower extremities. Blood pressure in the right arm was 120/70 torr. Routine laboratory tests, coagulation studies, and chest radiogram were within normal limits except for the fasting blood glucose of 350 mg/100 ml. ECG showed sinus rhythm, a rate of 95/min and nonspecific ST-T wave changes in leads I and AVL, similar to those noted 2 years previously.

The patient was premedicated intramuscularly with meperidine, 25 mg, hydroxyzine, 25 mg, and atropine, 0.4 mg, 60 minutes preoperatively. On arrival in the operating room, the blood pressure on the right arm obtained by auscultation with a stethescope, was 124/70 torr. However, since the planned surgery involved the right upper extremity, the only site at which the blood pressure was recordable, and because direct arterial cannulation in the other extremities appeared to be difficult if not impossible, the right superficial temporal artery was located by palpation (Figure, A); a Doppler transducer was then positioned over the artery (Figure, B) and fixed in place with adhesive tape (Figure, C). A Kidde tourniquet cuff, 4 inches wide, was placed around the head (Figure, D) taking special care to avoid the eyes, and the transducer and the cuff connected to an ultrasound blood pressure instrument (Arteriosonde 1010) which was

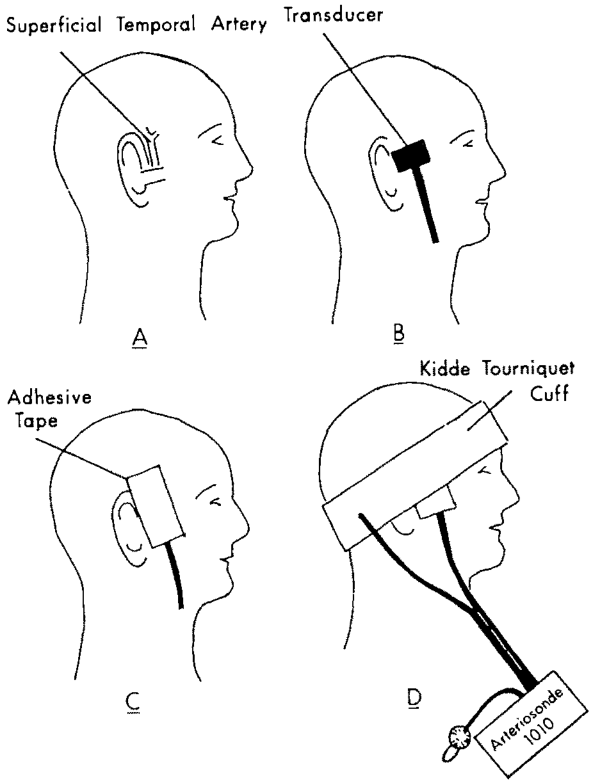

FIGURE. Techniques for use of Doppler ultrasonic flow probe over the superficial temporal artery: A, anatomy of superficial temporal artery; B, transducer in place; C, transducer fixed securely with adhesive tape; D, Kidde tourniquet cuff placed on the secured transducer.

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TABLE

Comparison of Blood Pressure at Brachial Artery (by Fiva-Rocci Cuff and Stethoscope) and at Superficial Temporal Artery (by Kidde Cuff and Doppler) in Normal Volunteers

	Volunteer no.									
	1	2	3	4	5	6	7	8	9	10
Sex	F	F	M	M	F	M	M	F	M	M
Age (years)	20	35	30	50	25	35	62	65	30	50
Site of BP determination										
Brachial artery	90/70	110/90	125/85	145/90	120/70	135/85	160/100	170/100	120/70	140/90
Superficial temporal artery	80/60	110/90	120/80	150/100	105/80	130/90	150/90	155/100	110/60	125/75

utilized for blood pressure measurements throughout anesthesia and surgery.

Following denitrogenation and intravenous administration of *d*-tubocurarine, 3 mg, anesthesia was induced slowly with droperidol, 5 mg, and thiopental, 100 mg, by intravenous injections. Endotracheal intubation was performed following succinylcholine, 100 mg. Maintenance of anesthesia was with nitrous oxide oxygen (60%/40%) and intermittent increments of 0.025 mg of fentanyl. Pancuronium was used for relaxation, and ventilation was controlled with a volume-limited ventilator.

Blood pressure was monitored at 10- to 15-minute intervals, except during periods of hemodynamic instability when the recordings were made more frequently. The patient's operative course was uneventful. Blood loss was estimated to be 500 ml. No complications attributable to the technique of blood pressure monitoring were noted postoperatively.

Discussion

The method described, that of recording the blood pressure with a Doppler device at the superficial temporal artery, is simple, non-invasive, and easily applicable to any adult patient. Although not frequently indicated, the method can be most useful in the care of burn patients whose burned extremities cannot be used or whose unaffected extremities are being used for graft tissue. With regard to details of the technique, a narrow inflatable cuff must be firmly fixed in the fronto-occipital plane avoiding the eyes. In length it must be at least 1½ times the circumference of the head if it is to remain securely in place when inflated. The Kidde cuff satisfies these requirements.

In using the Doppler on the superficial temporal artery, the values obtained for the systolic and diastolic pressure were within −15 to +10 torr of the values obtained in the arm using a stethescope in 10 volunteers (Table).

In summary, a method is described for recording blood pressure by Doppler principle using the superficial temporal artery. This method is accurate, simple, non-invasive and specially applicable to patients in whom the conventional sites cannot be utilized.

ACKNOWLEDGMENTS

We thank Drs. Gertie F. Marx and James Marin for help in the preparation of this manuscript. The continued encouragement of Dr. Louis R. Orkin is gratefully acknowledged.

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Cardiac Arrest during Cesarean Section in a Chronic Amphetamine Abuser

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George Albright, MD[*]

There has been general concern but little documentation among anesthesiologists that interactions between general anesthetic agents and drugs of abuse such as amphetamines may lead to sudden cardiovascular collapse.[1,2] In fact a recent textbook commented on the fact that there were no case reports in the literature concerning abnormal reactions in amphetamine users during anesthesia and surgery.[3] We present the case of a patient who sustained a cardiac arrest during cesarean section in which the primary cause of the arrest may have been due to chronic drug abuse.

Case Report

A 27-year-old black gravida 5 para 3 was admitted to Stanford University Hospital at term and in active labor. Past medical history was significant in that she had been a drug abuser of many years standing. As far as could be ascertained the main drugs of abuse had been heroin and amphetamines. She denied any recent drug usage. She had had three low transverse cesarean sections in 1964, 1967, and 1973 under regional anesthesia without complication. Clinical examination was negative except for the presence of sclerosed veins in both arms, and a history of vomiting for 12 hours prior to admission to hospital. There were no clinical signs of dehydration.

Continous epidural anesthesia was planned for the cesarean section. An epidural catheter was easily inserted at the L3-L4 interspace. Following a test dose, 10 ml of lidocaine 2% with epinephrine 1/200,000 was injected through the catheter and a T_{12} level of analgesia was obtained.

About 45 minutes later the patient was transferred to the delivery room. Chloroprocaine 3%, 12 ml, without epinephrine was injected through the catheter in preparation for operation. Ten minutes later because of an inadequate level of analgesic block (T_{12}) a second injection of chloroprocaine (6 ml of 3% solution) was given. No analgesic effect was noted. It was then decided to induce general anesthesia. Twenty minutes after the second injection of chloroprocaine general anesthesia was induced. At time of induction of anesthesia the systolic blood pressure was 100 torr, the pulse rate was 80 beats/min and the ECG showed sinus rhythm. Following left uterine displacement, preoxygenation, atropine (0.5 mg) and precurarization (curare 3 mg), thiopental, 200 mg, and succinylcholine, 100 mg, were injected intravenously, cricoid pressure was applied and endotracheal intubation performed. Following an easy intubation both lung apices moved well, equal breath sounds were heard bilaterally. The pulse rate was 110 beats/min and the systolic blood pressure was 120 torr. ECG showed sinus rhythm. Oxygen 2 L/min and nitrous oxide 4 L/min were begun together with positive pressure ventilation. The operation commenced immediately following intubation at which time it was noted that the patient's tongue was dark in color and examination of the operating field disclosed the presence of very dark blood. Nitrous oxide was discontinued and the heart sounds which previously had been well heard via a precordial stethoscope disappeared. No pulse was felt in either the radial or carotid arteries and no blood pressure could be obtained. At this time both pupils were dilated and the ECG was a flat line. Cardiopulmonary resuscitation (CPR) was begun immediately using external cardiac massage. This produced a palpable carotid pulse. Drugs used for treatment of the cardiac arrest included sodium bicarbonate, 100 meq, epinephrine 1/10,000, 5 ml, isoproterenol hydrochloride infusion, 2 μg/min, and decadron, 8 mg. Sinus tachycardia occurred about 8 minutes after resuscitation and brachial blood pressure was palpable at 60 torr. Coincidental with the resuscitation, a healthy 3 kg male infant was delivered. The Apgar score at 1 minute was 7. Fifteen minutes after CPR had commenced the pupils started to respond to light pulse and blood pressure returned to pre-induction values. Five minutes later the patient began to breathe spontaneously. An arterial blood sample obtained during the arrest showed pH 7.41, P_{CO_2} 27 torr, pH_{CO_3} 17.0 meq/L, and P_{O_2} 77 torr. About 90 minutes after the onset of the cardiac arrest she was returned to the intensive care unit awake but disoriented. She was later extubated and vital signs remained stable. Two days later she elaborated on her drug history. She had been taking amphetamines since age 13 and had continued to take them both intravenously and orally up to time of her admission to the hospital. Her use of heroin was intermittent; she last took heroin about 7 days before hospital admission. Toxicologic analysis of her urine obtained the

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day after her arrest showed levels of amphetamine and methamphetamine of 0.4 and 0.2 μg/ml, respectively These figures indicated only that amphetamines had been taken; they do not indicate either when the last amphetamine was taken or the amount taken. The patient was discharged on the sixth postoperative day with no apparent sequelae from her cardiac arrest.

Discussion

Unexpected cardiac arrest is one of the most dramatic and frightening events that can occur in the operating room. When it occurs in the delivery room during a cesarean section it becomes doubly threatening, for not one but two lives are threatened. Previous studies indicate that the incidence of cardiac arrest in the operating room varies from 1/800 to 1/3,400 operations.[4] The paucity of articles in the literature on cardiac arrest in previously healthy obstetrical patients undergoing cesarean section indicates it is a rare occurrence.

Possible causes for the cardiac arrest in this patient include high epidural block, aortocaval compression, light anesthesia, anesthetic overdose, and drug interaction. A less common cause of cardiac arrest would include a pulmonary embolus from either air or amniotic fluid.

Aortocaval compression by the gravid uterus is a well documented cause of maternal hypotension especially when combined with profound sympathetic blockade from a high epidural block. However, it was believed that neither of these two factors played any part in the cardiac arrest as the epidural anesthesia was ineffective and the blood pressure was stable, both of which makes it unlikely that the two factors were related to the cardiac arrest. Furthermore, precautions had been taken to prevent aortocaval compression. It was felt that the catheter probably become dislodged from epidural space during transportation of the patient to the operating room.

Light anesthesia can lead to an outpouring of catecholamines with consequent ventricular premature contractions, ventricular tachycardia, and finally ventricular fibrillation. However, the stability of the vital signs following induction and intubation made this sequence an unlikely cause of cardiac arrest.

A drug reaction from inadvertent intravenous injection of the chloroprocaine solution was considered. This was considered an unlikely cause of the cardiac arrest as a drug reaction would be expected to occur within seconds of injection.

Pulmonary embolus from either air or amniotic fluid is rare and did not fit the clinical picture. Consequently it was suspected that the drug abuse contributed to the arrest.

There is evidence from histochemical, biochemical, and pharmacologic studies that acute amphetamine administration leads to release of catecholamine from adrenergic nerve terminals both in the central nervous sytem and peripherally.[5-8] Experiments in dogs have shown that acute amphetamine intoxication significantly increases mean alveolar concentration (MAC) for halothane.[9] On the otherhand, chronic administration of dextroamphetamine, 5 mg/kg/day for 7 days, decreases MAC for halothane by 21 ± 5%.[9] The latter was believed to be due to depletion of central nervous system catecholamines. The clinical implications are 2-fold in the chronic drug abuser. First, the patient's anesthetic drug requirements may be less than in a nonaddicted patient, should halothane be used; and, second, patients taking amphetamines may respond poorly to the usual doses of indirectly acting sympathomimetic agents.

Our patient also had a history of heroin abuse, though the drug was used less frequently than the amphetamines. Hypotension in narcotic users is not unusual, with blood pressure levels as low as 50/20 torr even before induction of anesthesia.[10] However, narcotic users seem to tolerate anesthesia well, and, in fact, may need higher doses of anesthetic agents than nonusers. During maintenance of anesthesia, hypotension may develop because of inadequate blood levels of narcotic or because of adrenal insufficiency.[11] Preoperative or intraoperative administration of a narcotic will eliminate hypotension associated with narcotic withdrawal. Morphine has a depressive action on adrenocortical function and 17-hydroxycorticosteroid blood values are decreased in opium addiction. It is likely that long-term narcotic useage may lead to adrenocortical suppression and impaired adrenal response to surgical stress.[12] Should volume replacement, narcotics, and direct acting vasopressors fail to increase the blood pressure then hydrocortisone, 100 mg IV, may help to restore the blood pressure to normal levels.

It was felt, but difficult to prove, that chronic catecholamine depletion played an important role in this patient's cardiac arrest. It is postulated that the sequence of events could have been as follows. The chronic use of amphetamine led to an inability to respond to the stress of induction of anesthesia. Thiopental induction of anesthesia led to an increase in venous capacitance, a decrease in pre-load, a decrease in cardiac output and thus to cardiac arrest. It may be that in the chronic drug abuser clinical assessment of function of the sympathetic system may be of value in detecting patients at risk from autonomic insufficiency. Symptoms and signs that point to abnormalities of the sympathetic system include orthostatic hypotension and failure of the pulse rate to increase when the patient assumes an erect position. Valsalva's maneuver or exhalation against a closed glottis in a patient with an abnormal sympathetic pathway will not show the usual increase in heart rate during the period of increased intrathoracic pressure; also the phenomenon of systolic and diastolic overshoot are absent.[13]

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Drug-Induced Disorders of Neuromuscular Transmission

More than 30 drugs in current clinical use, other than those used in anesthesia, may interfere with neuromuscular transmission. The most common clinical presentation reported has been postoperative respiratory depression. Antibiotics, particularly those of the aminoglycoside group have been the drugs most frequently implicated, but many other drugs may interfere with neuromuscular transmission in the perianesthetic period. Unmasking or aggravation of myasthenia gravis is a second possible clinical presentation. In addition, several drugs may cause a reversible myasthenic disorder in patients with no evidence of a preexisting defect of neuromuscular transmission. Mechanisms of interference with neuromuscular transmission include either a direct effect on the various components of the neuromuscular junction or an immunologically mediated reaction directed against the motor end plate. Supportive therapy as appropriate, plus correction of associated abnormalitites (e.g., acid base, electrolyte) is advocated as the primary approach to treatment. In some circumstances, specific therapy may be indicated. *(Argov Z, Mastaglia FL: Disorders of neuromuscular transmission caused by drugs. N Engl J Med 301:409–413, 1979)*

letters TO THE EDITOR

More on Intravascular Migration of an Epidural Catheter

To the Editor:

We read with interest the article by Ravidran et al (Apparent intravascular migration of an epidural catheter. Anesth Analg 58:252–253, 1979). Since this complication of epidural analgesia is uncommon and rarely reported, we submit the following case to collaborate the experience of the above authors.

A 26-year-old healthy primigravida at term with no history of seizure disorder had an epidural catheter placed at L2-3 to manage the discomfort of labor and vaginal delivery. The local anesthetic solution utilized consisted of equal parts of 0.75% bupivacaine and 3% 2-chloroprocaine (0.375% bupivacaine, 1.5% 2-chloroprocaine). After negative aspiration, 2 ml were injected through the catheter followed in 3 minutes by an additional 6 ml. Aspiration of the catheter for blood and cerebrospinal fluid (CSF) following each injection was negative. Within 15 minutes the patient was pain-free with an upper T_{10} sensory level bilaterally. Two hours later when the patient again became uncomfortable, a 2-ml test dose was given through the catheter with negative aspiration for blood and CSF. This was followed in 3 minutes by 8 ml of the local anesthetic solution. Within 15 seconds the patient described a vague, very brief "heaviness" which was followed immediately by a grand mal convulsion lasting about 30 seconds. The seizure, which subsided spontaneously, was managed with oxygen and control of the airway. The patient became responsive to voice in about 90 seconds, and 1 minute later she was rational. Following the convulsion, the patient's vital signs remained stable, but the fetal heart rate showed some mild variable decelerations during several contractions following the convulsion. No level of anesthesia was established. While blood could not be aspirated, on removal of the catheter frank blood was present in the catheter tip. Although a venous blood sample was not obtained for bupivacaine levels, all the above indicate the second injection was made intravascularly.

This case emphasizes that aspiration through an epidural catheter or the injection of a small test dose of local anesthetic will not always indicate the intravascular placement of the epidural catheter.

Since this episode, we have modified our usual technique so that following the customary 2-ml test dose (to indicate subarachnoid injection) the therapeutic dose is not injected as a bolus but instead is given in 5-ml increments, pausing for 30 seconds each time to assess subjective symptoms. We stress that even with these precautions accidental intravascular injection may occur, requiring the presence of a trained physician along with proper resuscitation equipment.

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"Bedbug Infestation" as a Complication of Epidural Anesthesia

To the Editor:

Although much has been written dealing with complications associated with spinal or epidural anesthesia, little of this has been concerned with related procedures, such as testing for segmental sensory loss with pinprick. The following case illustrates one such problem.

A 78-year-old man, 175-cm tall, weighing 92 kg, presented with obstructive uropathy for which a suprapubic cystostomy was indicated. The preoperative assessment disclosed no allergies or recent medications. There was a history of hypertension, chronic productive cough, and shortness of breath as well as chest pain associated with exertion.

An epidural anesthetic was performed at the L3-4 interspace using 1.5% lidocaine with 1/200,000 epinephrine. The level of anesthesia was determined by the patient's lack of perception of sharpness when pricked by a disposable 18-gauge needle. After approximately 10 minutes the level was T_5 and the subsequent anesthetic and operative course were uneventful.

On the day following surgery, the surgical resident made note of "multiple purpuric lesions approximately 5-mm wide with central punctate lesions, noted in a linear pattern along both thighs and pretibial area. Appears consistent with pruritic insect bites" (Fig 1). Further consultation was obtained and the dermatology resident "confirmed" that these were, indeed, bedbug bites. However, 5 days later the dermatologist wrote that the "purpuric lesions were apparently secondary to pinpricks dur-

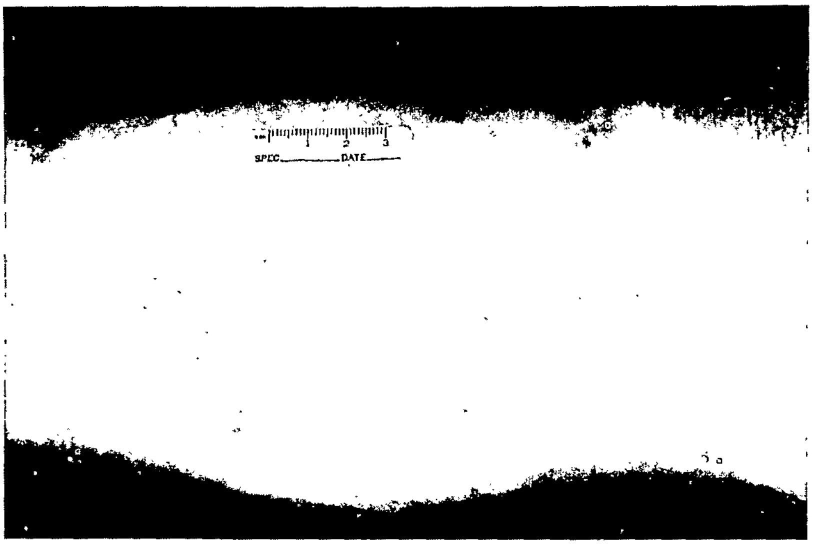

FIG 1. Patient's leg on the first postoperative day. Multiple lesions approximately 5-mm wide were noted over the thigh and pretibial area.

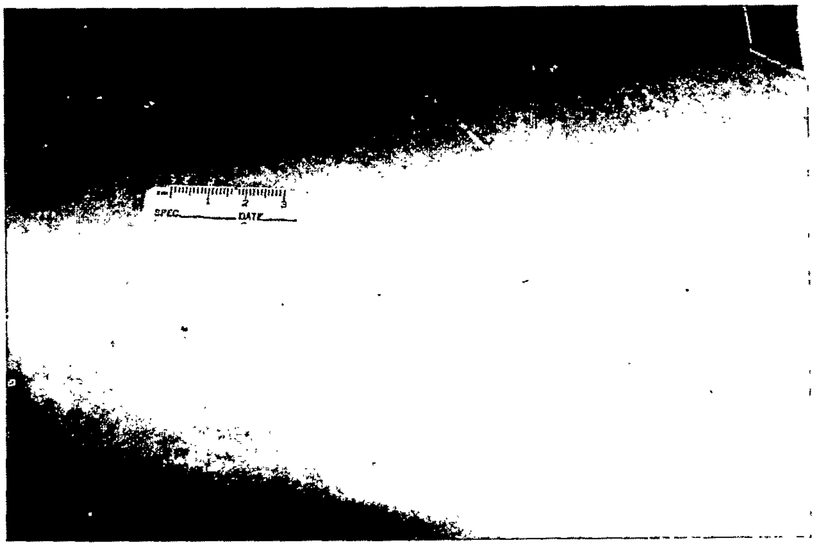

FIG 2. Patient's leg 5 days later. The linear track of the lesions is easily seen.

ing anesthesia's testing of adequacy of spinal anesthesia." Apparently, someone had noticed the length of the lesions' linear tracks (Fig 2) and had speculated on a source more likely than bedbugs.

On examination, the patient was found to have multiple circular erythematous lesions, each 4 to 5 mm in diameter. They were not elevated and now had faded to a brown color. Each had a linear puncture extending from the center to an edge. On the left, they ran in a single line from mid to upper thigh, each one regularly spaced several centimeters from the next. Two small clusters were noted on the right, one on the lateral thigh and one over the tibia. No examination of the abdomen was made. The punctures were neither circular nor central, nor were they crusted or of variable size. Thus, the likelihood of their association with scabies or bedbugs were remote. They matched in size and shape the sort of punctures that would be made by the beveled end of an 18-gauge disposable needle. It is entirely possible that such punctures might result from excessive or carelessly applied force or as a result of unusually fragile skin, particularly when one considers the extremely sharp edge carried by most single-use needles.

A review of several texts dealing with regional anesthesia disclosed no mention of this sort of problem, even though testing for loss of sharp sensation was prominently mentioned as a satisfactory method of evaluating analgesia. It may be significant that none of the authors referred to the use of disposable needles, although some made considerable mention of reusable equipment. It is possible that the trend toward increased use of disposable needles raises a risk of superficial skin puncture that was not so prominent with multiple-use equipment.

An alternative method for evaluating the level of analgesia is use of an alcohol-soaked swab. This may be applied to the skin to determine the level at which temperature discrimination is lost. Although this level may not correspond to the uppermost site of acceptable surgical analgesia, we found a clinically satisfactory correlation between testing for pain and cold when these two modalities were compaired 15 minutes after induction of spinal anesthesia. This good relationship makes the testing of the level of analgesia with an alcohol swab an attractive alternative to the use of pinprick, particularly in view of our recent "infestation."

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book REVIEWS

Development of New Volatile Inhalation Anaesthetics, edited by A. B. Dobkin, Amsterdam, Elsevier/North - Holland, 1979, 370 pp, $70.25.

The late Dr. Dobkin states in the preface "... a tremendous amount of investigation has taken place over the last few years to determine the properties of these (volatile) agents. It is hoped that this volume will provide an authoritative guide to and a useful review of the tremendous amount of work ... of the past ten or fifteen years." This book does fulfill that goal. His own numerous publications, especially on enflurane and isoflurane, are the background for a large portion of the book. However, all the chapters on the individual agents are extremely well referenced and a wealth of data is presented about the halogenated agents and the many controversies they engender.

The volume begins with a brief review of the older agents such as divinyl ether and chloroform, and proceeds through individual chapters on newer halogenated volatile agents. Most of the latter were written by the editor and thus are of uniform style. Next are several chapters on investigational drugs, one chapter by Van Dyke on biotransformation, a brief summary of the toxicities of the agents, and a useful discussion of vaporizers.

The reviewer would have liked a separate chapter on the principles of upfake and distribution of volatile agents at the beginning of the book. Instead nearly every chapter has a section discussing uptake and distribution but never in sufficient detail. The ready availability of that information from other sources may have persuaded the editor that his book did not require it.

The criticisms are minor and this book would be a fine addition to departmental libraries. With the large bibliography, it makes an excellent reference on the volatile agents.

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Pharmacology of Respiratory Therapy Medications, by M. J. Strauch, Chicago, Yearbook Medical Publishers, Inc, 1979, 249 pp, $14.95.

The book *Pharmacology of Respiratory Therapy Medications* starts well and has good stated purposes but certainly does not achieve these objectives. It was designed to be an outline of the pharmacology of medications used in the field of Pulmonary Medicine. It would appear that the author collected package inserts, promotional items from drug companies, "throw away" medical journals, items from the Physician's Desk Reference (PDR) and other similar sources. This was semiorganized into categories of drugs with similar actions, outlined, and then put into the form of a manuscript. One or two chapters, for example the one on sympathomimetic drugs, came together well. The others are characterized by incompleteness, inaccuracies, generalization based on conjecture and other authors' opinions. The latter problem is dangerous to the uninitiated who might read the book and think it is authoritative.

There are many individual problems, a few of which will be cited. The author assumes some knowledge of chemistry, yet is unwilling to decide which chemical formula is correct, so he presents both. Chapters on experimental drugs such as marijuana and glucagon, are brief but do not belong in a book of this type. The chapter on steroids includes a dissertation on why one should not inject these drugs into joints repeatedly. This must have slipped by the editors. The chapter on "asthma" is misleading in its briefness and might better be excluded. Many other examples could be presented.

The text might have served as a ready reference, or as an outline for a lecture series for respiratory therapists but the omissions, editorial oversights, poor organization, and inaccuracies might prove a problem for the beginner. Anesthesiologists and chest physicians ought to have a better ready reference than this.

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Clinical Simulations for Respiratory Care Practitioners, by D. C. Assmann, S. J. Hixon, and R. M. Kacmarek, Chicago, Yearbook Medical Publishers, 1979, 175 pp, $22.50.

Clinical Simulations for Respiratory Care Practitioners is filling the void for respiratory therapists preparing to take the national clinical simulation. The authors have been instrumental in developing for the National Board for Respiratory Therapy the examination that is now a requirement for becoming a registered therapist.

The format of the book is well conceived. It begins with an introduction to clinical simulations, develops to the content of a sample problem, and ends with six actual problems. The method of presenting the practice problems is beneficial because it uses a latent image system that is the same form as the national simulation. The reader is able to take the test, score it, and compare his score to minimum passing levels. The person scoring the problem is not only able to see the optimal route through the question, but can follow alternate pathways which could still give a passing score. This is well presented in the analysis following each problem. The test deals in a point system of a positive to a negative value for each response. The analysis gives the score for each response and briefly explains why the questions have that partiuclar value.

I would highly recommend this book for anyone preparing for the clinical simulation offered by the National Board for Respiratory Therapy.

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Cardiovascular Function Principles and Applications, by F. L. Abel and E. P. McCutcheon, Boston, Little, Brown and Co, 1979, 424 pp, $35.00.

This book provides a comprehensive review of cardiovascular physiology and instrumentation for the postgraduate student in physiology and medicine. According to the preface, this text is intended to supplement basic information and not to serve as a complete and all-inclusive reference in the area of cardiovascular physiology. A major thrust of the entire text is instrumentation, especially in the research laboratory. The authors have provided an excellent overview of methods of data acquisition and their interpretation.

Cardiovascular Function is subdivided into four general areas: (1) cardiovascular measurements, (2) cardiac function, (3) the vascular system, and (4) circulatory integration and regulation. These subgroupings do not encompass the entire field of cardiovascular physiology, but each portion is thorough in its limited scope. Thus, the section on cardiac function includes a very detailed review of electrical and mechanical properties of cardiac muscle and covers some electrocardiography. In addition, a thorough review of cardiac muscle physiology is discussed with a correlation of ventricular performance.

The book is well written and comprehensively details the selected areas. The authors' styles are dry and the reading slow by the very nature of the subject material. Since the authors are primarily physiologists, the major theme of this text deals with muscle preparations, in vitro methods, and laboratory data acquisition and interpretation. Very little in vivo data are presented and almost no clinical correlation is attempted. No mention is made of the Swan-Ganz catheter, cardiac outputs by thermodilution, noninvasive measurements of contractility, or other modern operating room or intensive care unit monitoring techniques. For the physician involved in day-to-day patient care or the general anesthesiologist, this book serves a very limited role. For the cardiac anesthesiologist, intensivist or cardiologist, this text can provide a useful intermediate source of reference for research projects, as long as its clinical limitations are realized.

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Mode of Action of Autonomic Drugs, by B. D. Bhagat, Flushing, New York, Graceway Publishing Co, 1979, 170 pp, $21.50.

This is a very basic and easy to understand synopsis of the autonomic nervous system. The chapters on "Synaptic Transmission" and "Synthesis, Storage and Inactivation of Transmitter," are a good review of both the basic physiology and pharmacology of the autonomic nervous system.

The remaining chapters discuss drugs as they affect the autonomic nervous system. The description of these drugs is superficial and inadequate in depth or detail. There are minimal references to clinical situations and most of the drugs are discussed in a superficial manner. Generally, the description of the pharmacology of the drugs does not point out any advantage of one drug, such as neostigmine, over another, such as physostigmine. This superfiical discussion without sufficient detail limits the book's value to the practicing anesthesiologist. Another example of the latter is that echothiophate iodide is stated to be a long acting cholinesterase inhibitor, but no mention of its clinical relevance with the use of succinylcholine is mentioned.

Another major drawback of this monograph is that very little detail is provided regarding the use of drugs in the treatment of pathologic states. Minimal mention is made of the dose required of the various sympathomimetic amines and the differing response depending upon the dose administered. An example: dopamine is mentioned and its effects are stated at a dose of 10 μg/kg/min. The effect of different doses is not discussed. Also, there is no mention of dobutamine in this monograph. The lack of detail in the discussion of the sympathomimetic amines limits the clinical usefulness of this book for the practicing anesthesiologist.

The chapter on the adrenergic blocking drugs is again quite superficial. An example: the central effects of alpha-methyl-dopa are only transiently mentioned, while its function as a false transmitter is stressed. Another example is that no mention is made regarding anesthesia and the use of monoamine oxidase inhibitors. Generally, most of the drugs presented as adrenergic blocking drugs are covered in insufficient detail to be of value to the anesthesiologist.

Lastly, the chapter on the "Neuromuscular Blocking Drugs" is of questionable value. An example: decamethonium and succinylcholine are presented together and no differentiation between the pharmacologic effects of the two drugs is mentioned. Pancuronium bromide is not even mentioned.

In summary, this is a brief monograph on the autonomic nervous system. It covers the basically accepted anatomy and physiology reasonably well. When it comes to the drugs that affect the autonomic nervous system, the coverage is very superficial and of inadequate depth to be of value to the anesthesiologist. This monograph also suffers from the lack of references and the absence of an index.

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Lecture Notes on Anaesthetics, by J. N. Lunn, London, Blackwell Scientific Publications, 1979, 170 pp, $9.95.

Dr. Lunn has attempted to summarize all the things an undergraduate needs to know about "anaesthetics" in this 170-page paperback which is one of a series of *Lecture Notes* published by Blackwell. His objectives in teaching undergraduates are set out in the beginning.

> The student should become aware of the role of an anaesthetist and the scope of anaesthsia and intensive care, understand all aspects of the management of the unconscious patient, appreciate the implications of intercurrent general medical disease in association with surgery and anaesthesia, acquire and practice skills of venepuncture, airway maintenance and manual ventilation of the lungs, be introduced to the skills endotracheal intubation and other manoeuvres.

As an adjunct to clinical experience the book might be useful but it falls short of providing by itself the sort of summary of anesthesiology that I would recommend to students. The first chapter on preoperative assessment is promising but the rest is disappointing. Cardiovascular and chest diseases are selected as examples of conditions that have profound anesthetic implications. But after noting that the presence of angina or the occurrence of a myocardial infarction within 3 months is of grave import he dismisses the problem with, "there is not much knowledge about prophylaxis against postoperative infarction but adequate analgesia with consequent freedom from stress would seem to be an important matter."

The assessment of the patient with pulmonary disease was more detailed and, one felt, more familiar ground for the another. Diabetes, obesity, skeletal disease, liver disease, anemia, current drug intake, and the history of previous anesthetics were discussed briefly but adequately.

The rest of the book is devoted to the pharmacology and physiology of anesthesia, techniques (much of which will puzzle Americans unfamiliar with the Magill apparatus), coma, and a final chapter on the subspecialties of anesthesia. There is an appendix containing definitions and reference values and an index.

It's tough going. The style is turgid; sentences are clumsily composed; and the organization of topics leads to confusion. The chapter on coma, for instance, mixes the management of all kinds of unconsciousness together so that no clear picture of general anesthesia emerges. But my major dissatisfaction is with the emphasis on the technicalities peculiar to anesthesiology. A book for nonanesthetists need not dwell on the dreary details of the gas laws or rebreathing systems unless it is to illustrate a point. The really interesting problems of modern anesthesia practice that might capture the imagination of students should be the major lessons instead of being briefly mentioned under "A miscellany of special topics." It is tempting to cram everything the student ought to know into one book but the result is usually tedium and alienation. How much better it would be to present the topics that we anesthesiologists find fascinating. To do less is to underestimate the students.

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Management of Acute Intracranial Disasters, by R. V. Trubuhovich, Boston, Little, Brown and Co, 1979, 448 pp, $35.00.

Advancements in neurodiagnostic techniques and faster transportation of head-injured victims have resulted in greater numbers of critically ill patients surviving to require surgical intervention or prolonged neurologic supportive care. All anesthetic agents and techniques allow intracranial dynamics, and it therefore behooves the anesthesiologist to understand clearly the underlying cerebral pathophysiology.

Dr. Trubuhovich has gathered a distinguished group of international workers from several disciplines. The 17-chapter book is roughly divided into diagnosis, management, and special investigations that aid therapy.

There is marked inconsistency in clarity and depth between the contributions. Drs. Miller and Sullivan's chapter on severe intracranial hypertension is concise, well written, and referenced. Acute brain swelling is also adequately covered. Dr. Jennett's section on prediction of outcome as a basis for management decisions is also explicit and, refreshingly, combines philosophy with science.

Studies of nonoperative treatment of head injuries from New Zealand and Sweden are not truly comparable but the main conclusion "that, with the exception of controlled hyperventilation, variations in management details of severely head-injured patients may not be crucial in determining the outcome" is probably valid.

The literature on global brain ischemia is carefully reviewed by Dr. Safar who also gives us an exciting preview of prospective multi-institutional studies. Although intracranial pressure control by barbiturates in Reye's syndrome has been shown to be life-saving, the therapeutic regimen is afforded only brief mention.

The anesthetic management of missile injuries is poorly covered. Large doses of diazepam rather than thiopental sodium are suggested for induction and heavy reliance is placed on nondepolarizing muscle relaxants

(2 to 4 mg of pancuronium bromide per hour), tranquilizers, and narcotics. Pulmonary problems caused by intracranial hypertension are not defined.

Although the chapter on the management of relatives is sincerely written, it is simplistic and out of place.

The contribution on subarachnoid hemorrhage did not make the publisher's deadline and some makeshift notes were substituted which require that the reader refer to other sections throughout the book.

The chapter on electroencephalography as a selective aid in diagnosis has many helpful tracings. The usefulness and drawbacks of this tool are carefully defined and the authors honestly state that its "contribution is best when the nature of the pathology is known."

Monitoring of intracranial pressure is superficially covered. Moss and McDowall, in reporting their own experiences, found ICP monitoring to be of no value in determining the prognosis in individual patients. While this observation may be valid, it is not necessarily true in reviewing trend recording of intracranial compliance, a calculation which should be an integral part of continuous ICP monitoring.

Many illustrations of CAT scans combined with patient examples make a useful chapter.

The book contains much useful information for the anesthesiologist about underlying pathology in head injury; however, little guidance for specific anesthetic management or appropriate choice of respiratory supportive care is offered.

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Physiological Aspects of Anaesthetics and Inert Gases, by A. G. MacDonald and K. T. Wann, New York, Academic Press, 1978, 308 pp, $36.25.

The authors, who are physiologists, found the subject of anaesthetics and inert gases lacking a basic text. They, therefore, wrote this text for students of biological and biophysical sciences and of medicine, and attempted to describe the multitude of effects that anaesthetics, inert gases and similar substances exert in living cells and organisms. Although the title of this book implies broad coverage of physiological effects, the greater part of the text is concentrated on cellular or biochemical effects.

The contents are well organized with a table of contents in front of each chapter. Chapter 1 is especially helpful for laying out the substance of the entire text with definitions of terms to tune the reader into the proper wavelength, (e.g., narcotic-like effects and non-narcotic properties).

Chapter 2 deals with cell structure, movement, and division. This reader found this chapter heavy going, largely because of distant familiarity with protozoan and plant cytology. This was further complicated by description of the diverse effects of anaesthetics, inert gases and partial pressures on these unicellular species. Chapters 3 to 6 take the reader from biochemical actions of anaesthetics to anaesthetic effects on inexcitable and excitable membranes and on synapses. Only the final chapter on some non-narcotic aspects of anaesthetics and inert gases focuses on the *whole animal*.

The authors did an admirable job in providing a coherent presentation of an enormously diverse and complex subject. The format of presentation is far more appealing than the usual annual "reviews." The timely insertions of "summary and conclusion" periodically are very helpful in guiding the reader through the barrage of information. Figures and tables are generously distributed throughout the chapters and are satisfactory. The authors did not intend to provide comprehensive coverage of all of the subjects, rather a selected few. It is intended to be an introductory text, but much fundamental information is required of the reader in order to make this worthwhile reading.

In summary, I believe this is an excellent reference text for the academician, researcher, and graduate student, but only for the most interested and informed medical student or clinician.

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BOOKS RECEIVED

Principles and Practice of Blood-Gas Analysis, by A. P. Adams and C. E. W. Hahn, London, Franklin Scientific Products, 1979, 95 pp.

Advances in Pain Research and Therapy, Volume 3, by J. J. Bonica, J. C. Liebeskind, and D. G. Albe-Fessard, New York, Raven Press, 1979, 984 pp, $75.00.

Selected Papers in Respiratory Therapy, 2nd edition, by T. J. DeKornfeld, Garden City, New York, Medical Examination Publishing Co, Inc, 1979, 542 pp, $20.00.

Development of New Volatile Inhalation Anaesthetics, edited by A. B. Dobkin, Amsterdam, Elsevier/North-Holland, 1979, 370 pp, $70.25.

Applied Respiratory Physiology, 2nd edition, by J. F. Nunn, Woburn, MA, Butterworths Publishers, 1979, 524 pp, $39.95.

Modern Hospital, by E. Pütsep, London, Lloyd-Luke Ltd, 1979, 687 pp, $20.00.

Anesthesiology: A Manual of Concept and Management, 2nd edition, by C. W. Quimby, Jr., New York, Appleton-Century-Crofts, 1979, 384 pp, $12.50.

Nutritional Aspects of Care in the Critically Ill, edited by J. R. Richards and J. M. Kinney, New York, Churchill Livingstone, 1977, 668 pp, $29.50.

Manual of Pediatric Anesthesia, by D. J. Steward, New York, Churchill Livingstone, 1979, 305 pp, $15.95.

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Avery MA, Fletcher BD: The Lung and Its Disorders in the Newborn Infant. Third edition. Philadelphia, WB Saunders Co, 1974, pp 54–58

Chapter in Edited Book

Phillips OC, Capizzi LS: Anesthesia mortality, in Public Health Aspects of Critical Care Medicine and Anesthesiology. Edited by P Safer. Philadelphia, FA Davis Co, 1974, pp 219–224

Illustrations. Include one complete set of illustrations with each copy of the manuscript. Number illustrations in order of citation. On a label on the back, give figure number, first author's name, and arrow indicating top of figure.

Legends. Type legends on a separate page using double spacing.

Tables. Each table should be typed on a separate page and should include a brief descriptive title. Use double spacing. Do not duplicate in tables material also presented in text.

Alterations. The Journal will charge authors for excessive alterations (more than $25.00 per article) at the rate of $2.75 per occurrence.

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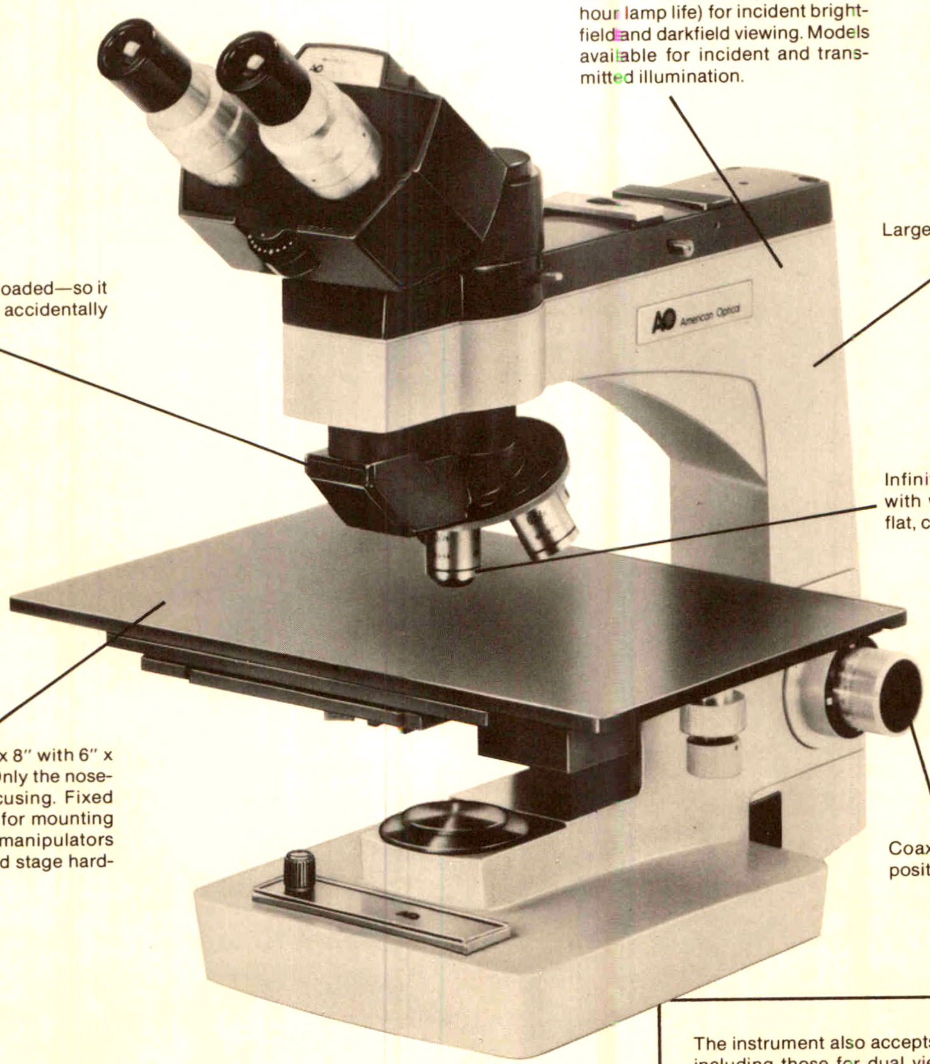

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References: 1. Brown, B.R., and Sipes, I.G.: Commentary: Biotransformation and hepatotoxicity of halothane. Biochem. Pharmacol. 26:2091, 1977. 2. Bunker, J.P., et al.: The National Halothane Study. Washington, D.C. Government Printing Office, 1969.

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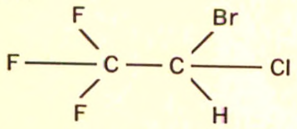
Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE (halothane, U.S.P.) is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE (halothane, U.S.P.) has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w).

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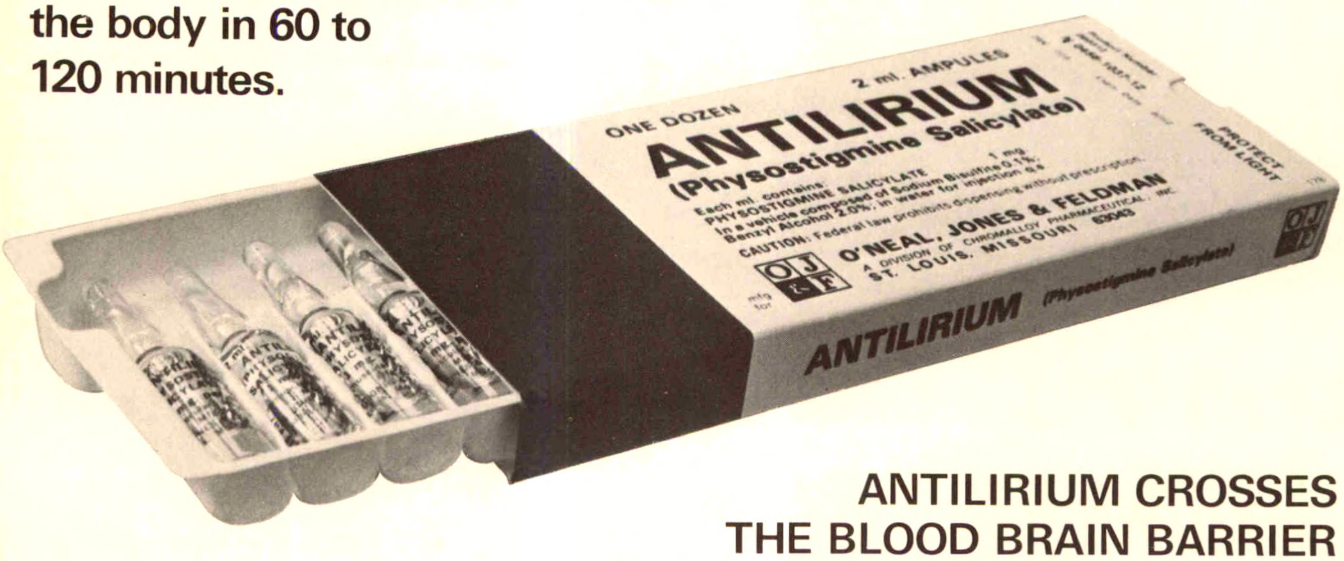
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Each ml. contains:
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In a vehicle composed of Sodium Bisulfite 0.1%, Benzyl Alcohol 2.0%; in water for injection q.s.

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. The action of acetylcholine is normally very fleeting because of its hydrolysis by a specific enzyme. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine. The changes in body function which are produced by the injection of physostigmine are, therefore, very similar to those which would occur from simultaneous stimulation of the parasympathetic nerves and include contraction of the pupil, increased tonus of the intestinal musculature, constriction of the bronchi and stimulation of secretion of the salivary and sweat glands.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quarternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Drugs with anticholinergic properties primarily antagonize acetylcholine competitively at the neuroreceptor site. Cardiac muscle, exocrine glands, and smooth muscle are most markedly affected. Action of the inhibitors is overcome by increasing the level of acetylcholine naturally generated in the body through inhibiting the enzyme (cholinesterase) which normally prevents accumulation of excess acetylcholine. It does this by hydrolyzing that compound to inactive acetic acid and choline. Agents which inhibit this enzyme, so that acetylcholine accumulates at the neuroreceptor sites, are called anticholinesterases.

Physostigmine, one of the anticholine esterases which is a tertiary amine, crosses into the central nervous system and can reverse both central and peripheral anticholinergic actions.

The anticholinergic syndrome has both central and peripheral signs and symptoms. Central toxic effects include anxiety, delirium, disorientation, hallucinations, hyperactivity, and seizures. Severe poisoning may produce coma, medullary paralysis, and death. Peripheral toxicity is characterized by tachycardia, hyperpyrexia, mydriasis, vasodilatation, urinary retention, diminution of gastrointestinal motility, decrease of secretion in salivary and sweat glands, and loss of secretions in the pharynx, bronchi, and nasal passages.

Some drugs in the anticholinergic group, such as imipramine and related tricyclics also produce additional toxic effects such as cardiac arrhythmias which can be reversed by physostigmine.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Toxic effects from mixed drug ingestions and combination preparations such as amitriptyline and perphenazine may respond less dramatically. Since physostigmine is rapidly metabolized, therapeutic doses may be necessary at intervals as life-threatening signs such as arrhythmias, convulsions, and deep coma recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

INDICATIONS: **TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.**

It has also been reported that ANTILIRIUM (physostigmine salicylate) may antagonize the CNS depressant effects of diazepam.

CONTRAINDICATIONS: Physostigmine salicylate injections should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents (decamethonium, succinylcholine).

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions. An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur. Physostigmine salicylate is rapidly metabolized in the body.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

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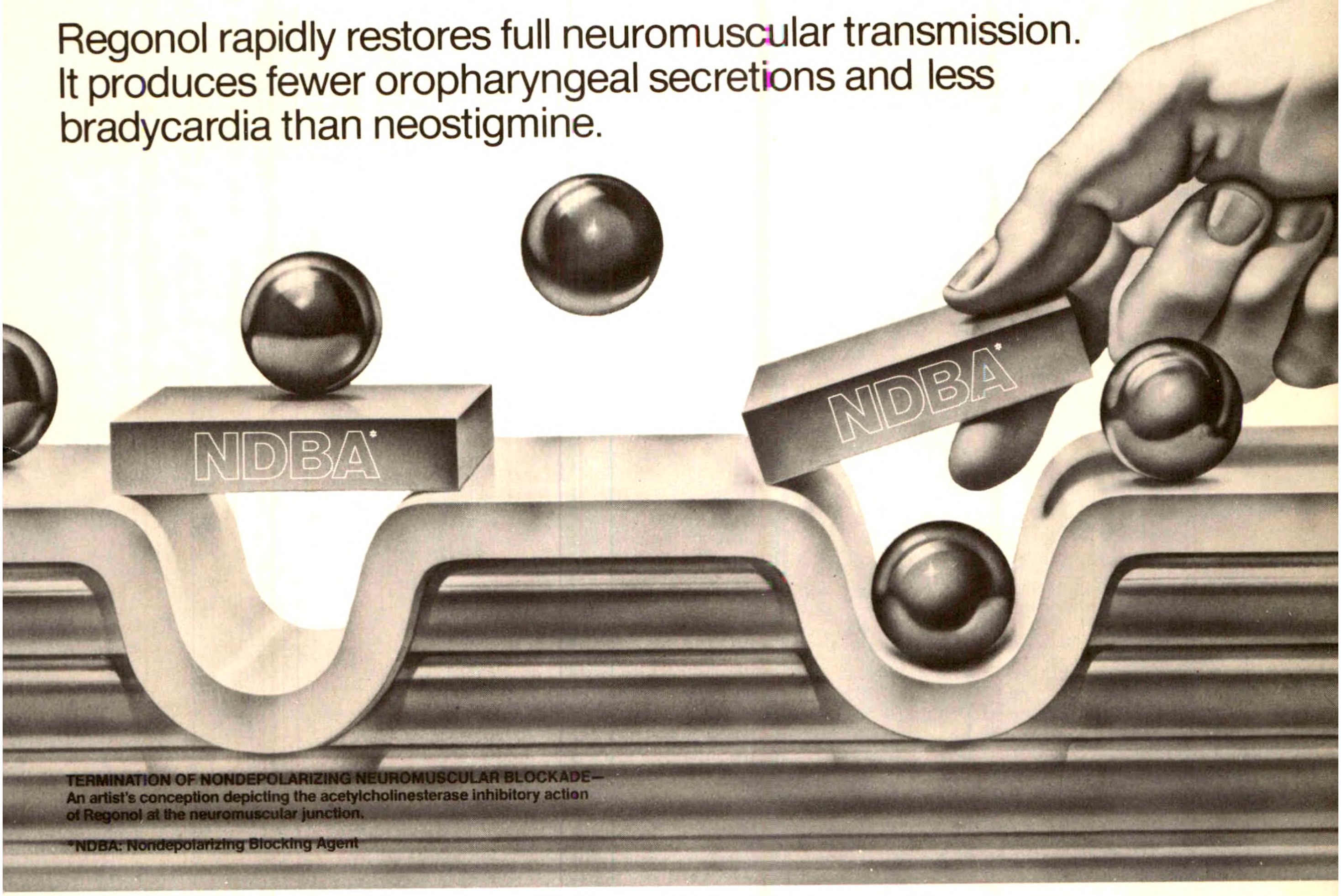

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